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Original Communications

CHANGING INDICATIONS FOR CESAREAN SECTION

Analysis of Fifteen Years' Experience at Flushing Hospital

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THE recent literature contains numerous articles justifying the increase in the incidence of cesarean section on the basis of broadening the indications for this type of delivery.[1-9] It has been estimated that 1.5 to 2 per cent of all women presenting themselves for antenatal care in the United States will have a cesarean section.[10, 11] These reports also show the incidence of cesarean section in private patients to be at least twice as great as in ward patients. While we are in agreement with some of the "broadened" or "new" indications, we are also aware that many of the "old" indications are no longer tenable. Since the incidence of cesarean section at Flushing Hospital decreased in the past 5 years compared to the previous 10 year period, in spite of the fact that repeat cesareans were twice as common in the last few years, we have analyzed our results with a view to ascertaining the factors involved in this decrease.

Incidence

From January, 1937, through December, 1951, there were 34,373 deliveries at Flushing Hospital, of which 1,303, or 3.8 per cent, were terminated by cesarean section. The incidence is shown in Fig. 1 for this 15 year period.

The incidence has ranged from 2.5 per cent to slightly under 5 per cent. We believe it is significant that the incidence in the past 5 years has been lower than in the previous two 5 year periods in spite of the fact that the percentage of repeat cesareans has more than doubled. The figures for the 5 year periods are shown in Table I.

TABLE I. INCIDENCE OF CESAREAN SECTION FOR FIVE-YEAR PERIODS

	1937-1941	1942-1946	1947-1951
Total deliveries	7,404	10,865	16,104
Cesarean sections	290	466	547
Per cent cesarean	3.9	4.2	3.4

What should the incidence of cesarean section be? We have tabulated the incidence of cesarean section at various obstetrical services in Table II.

The incidence in the various institutions varies from 1 to 10 per cent. McCormick[20] tabulated the incidence of cesarean section in 20 leading American clinics from 1941 to 1945, reporting 8,118 sections in a total of 244,369 deliveries, or 3.32 per cent, with a mortality rate of 0.61 per cent. The figures ranged from a low of 0.51 per cent to a high of 7.06 per cent. In these 20 clinics there was no direct correlation, however, between a low incidence of cesarean section and a low maternal mortality rate.

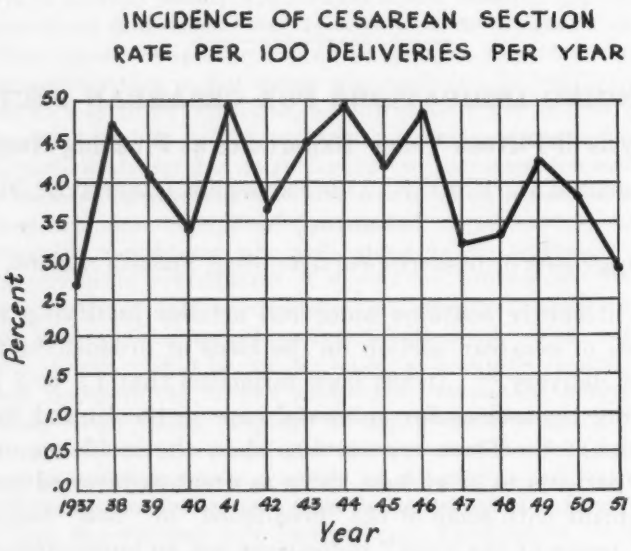

Fig. 1.

There must be a marked divergence of opinion in the treatment of obstetrical complications to result in so wide a discrepancy in the incidence of cesarean section. It is our impression that many tenuous and unwarranted indications are now masquerading as "broadened" indications. Colvin[21] has listed the following factors as tending to promote expansion of cesarean section: (1) increased hospitalization, (2) prophylaxis against infection, (3) improvements in operative technique, (4) influence of training centers, (5) roentgen-ray pelvimetry, (6) fetal safety, and (7) remuneration and convenience.

These factors have not contributed to the complete advantage of the patient. Although increased hospitalization for obstetric patients is to be commended, some hospitals offer a favorable environment for the unsupervised or the surgically trained operator to perform unnecessary sections. Compulsory consultation by two qualified obstetricians plus a discussion of each section at conferences would greatly reduce the incidence of cesareans in many hospitals. Too often roentgen-ray pelvimetry is offered as proof of cephalopelvic disproportion without an adequate trial of labor. The incidence in sections done for fetal distress is not infrequently based on the fallacious belief that delivery by cesarean section insures greater safety for the fetus. Do re-

TABLE II. CESAREAN SECTION INCIDENCE IN OTHER HOSPITALS

CLINIC	YEARS	TOTAL NO. DELIVERIES	NO. CESAREAN SECTIONS	INCIDENCE PER CENT
Sloane Hosp. for Women[1]	1942-1947	17,226	1,266	5.8
Cedars of Lebanon[3]	1930-1937	6,007	547	8.3
	1937-1950	19,068	2,070	9.79
St. Vincent's Hosp.[4]	1932-1946	15,429	536	3.47
New York Lying-In[7]	1932-1948	54,937	1,622	2.9
Jefferson Davis Hosp.[12]	1941-1950	22,296	231	1.03
Pittsburgh Hosp.[13]	1940-1949	10,499	118	1.09
Durham Univ. Hosp.[14]	1939-1948	11,335	163	1.43
Bronx Hospital[15]	1932-1942	20,763	494	2.4
Bellevue Hospital[16]	1940-1948	14,671	387	2.65
William H. Coleman Hosp.[17]	1944-1950	10,208	606	5.9
Toronto General[18] Private	1935-1949	18,005	1,166	6.4
Ward		13,728	294	2.14
Millard Fillmore Hosp.[19]	1945-1949	14,591	1,192	8.16

muneration and convenience influence the greater incidence of section in private patients compared to ward patients?

Indications

Comparison of indications for section from various institutions is not always possible because criteria for classification vary so greatly. It would be well if some attempt at standardization of the classification of indications for cesarean section were undertaken so that one could discuss comparable statistics. We have chosen the classification used by Dr. R. Gordon Douglas[22] which divides indications into six categories.

The indications for section at Flushing Hospital from 1937 through 1951 are shown in Table III, divided in three 5 year periods.

TABLE III. INDICATIONS FOR CESAREAN SECTION

	1937-1941		1941-1946		1947-1951	
	NO.	%	NO.	%	NO.	%
I. Contracted Pelvis and Mechanical Dystocia.—						
A. Contracted pelvis	53	18.0	121	26.0	74	12.8
B. Cephalopelvic disproportion	64	22.0	73	15.6	83	15.1
C. Dystocia due to faulty presentation	7	2.4	16	3.4	19	3.4
D. Dystocia due to tumor	8	2.7	13	2.7	11	2.0
II. Toxemia.—						
A. Pre-eclampsia	21	7.2	27	6.0	18	3.3
B. Eclampsia	5	1.7	2	0.4	3	0.5
C. Hypertensive disease	6	2.0	7	1.5	4	0.7
III. Previous Cesarean Section.—	48	16.7	147	31.5	222	40.6
IV. Hemorrhage.—						
A. Placenta previa	23	8.0	34	7.0	36	7.0
B. Premature separation of the placenta	9	3.0	8	2.0	27	5.0
V. Intercurrent Disease.—						
A. Heart disease	14	5.0	4	0.9	5	0.9
B. Tuberculosis	6	2.0	1	0.2	0	0
C. Diabetes	0	0	0	0	1	0.2
VI. Miscellaneous.—						
A. Previous vaginal plastic	3	1.0	6	1.5	11	2.0
B. Uterine inertia	6	2.0	3	0.6	10	2.0
C. Others	17	7.0	4	1.0	23	5.0

Contracted Pelvis and Mechanical Dystocia.—

A. Contracted pelvis: There has been a decrease of 50 per cent in this indication in the past 5 years compared to the previous 5 year periods at Flushing Hospital. At present no section is performed for contracted pelvis

unless x-ray pelvimetry confirms the clinical findings. We believe this regulation has tended to decrease the number of sections for contracted pelvis. Proof that this is often a tenuous indication is found in Wilson's[10] analysis of 167 successful vaginal deliveries among 498 women previously delivered by cesarean section. He found that contracted pelvis or cephalopelvic disproportion was listed as the indication in 30 per cent of the unnecessarily sectioned patients.

B. Cephalopelvic disproportion: From 1941 to 1951 cephalopelvic disproportion was the indication in about 15 per cent of sections compared to 22 per cent from 1937 to 1941 at Flushing Hospital. A section is no longer done for this indication unless two qualified obstetricians agree that the patient has had an adequate trial of labor. There is little agreement in the literature as to what constitutes a reasonable or adequate trial of labor and we do not adhere to any time limits. The judgment of the attending physician who remains at the patient's bedside and repeatedly examines his patient for the frequency and character of her contractions as well as for progress in dilatation of the cervix and descent of the fetus is more important than time factors. X-ray pelvimetry during labor will frequently yield valuable information as to whether to continue with the labor. We believe it is important to bear in mind that because a patient has delivered vaginally previously does not necessarily mean that she may not have cephalopelvic disproportion in a subsequent pregnancy because of a much larger infant.

C. Dystocia: Dystocia due to faulty presentation or to tumor has remained fairly constant over the 15 year period in our series. Their combined incidence has been about 5 per cent for each of the three 5 year periods. We believe that a fair number of faulty presentations will right themselves with the onset of labor and this is to be awaited. By the same token, pelvic tumors which may appear to block the passage of the fetus through the birth canal early in pregnancy may rise out of the pelvis and present no obstacle at term. It is not our practice to do a cesarean section in order to remove a pelvic tumor which does not obstruct labor.

Toxemia.—

A. Pre-eclampsia: Pre-eclampsia was the indication for cesarean section in 3.3 per cent of our cases in the past 5 years, or approximately one-half that for the previous 10 year period. This reduction in the incidence of section for pre-eclampsia was primarily due to the fact that we encountered fewer patients with pre-eclampsia in the past 5 years. Opinions still vary as to the proper treatment of pre-eclampsia. Our policy is to hospitalize such a patient and treat her conservatively. If she does not respond to conservative treatment and she is not a candidate for induction of labor, a cesarean section is performed. The last death we had from pre-eclampsia occurred 8 years ago in a patient who was sectioned the day following admission and who received large amounts of intravenous fluids postoperatively. She developed what we now describe as a "lower nephron nephrosis" and died of pulmonary edema.

It is our feeling that the use of intravenous Pitocin will enable one to induce labor in a larger number of patients with pre-eclampsia in whom induction was previously not felt to be possible. It has been our experience that if the Pitocin induction does not work the first time it usually will within the next 24 hours. Recently we have successfully resorted to this method to induce labor in pre-eclamptic patients on whom we previously would have done a section.

B. Eclampsia: Eclampsia has decreased to 0.5 per cent as an indication for section in the past 5 years. Since eclamptic patients are poor surgical risks, one often hesitates to subject them to abdominal surgery, even though we realize that until the uterus is emptied of both fetus and placenta the eclampsia may persist or recur. The question frequently arises as to how long to wait after

the convulsions are controlled before terminating the pregnancy. We suggest that within a very short time after the convulsions are controlled and while the patient is still heavily sedated, induction of labor with intravenous Pitocin should be started with or without rupture of the membranes. Even if such an induction fails the first time, it will likely prove successful at the next attempt and section can still be done if necessary.

Previous Section.—

Our incidence of repeat section as shown in Fig. 2 has risen from 16 per cent in 1937 to 1941 to 31.5 per cent from 1941 to 1946 and to 40.6 per cent from 1947 to 1951. The arguments for and against the dictum, "once a cesarean, always a cesarean," are well known. We realize the increasing incidence of repeat section is not a desirable situation. Even in the best organized maternity hospitals where vaginal delivery is permitted following section, 90 per cent of elective repeat sections were in private patients.[10]

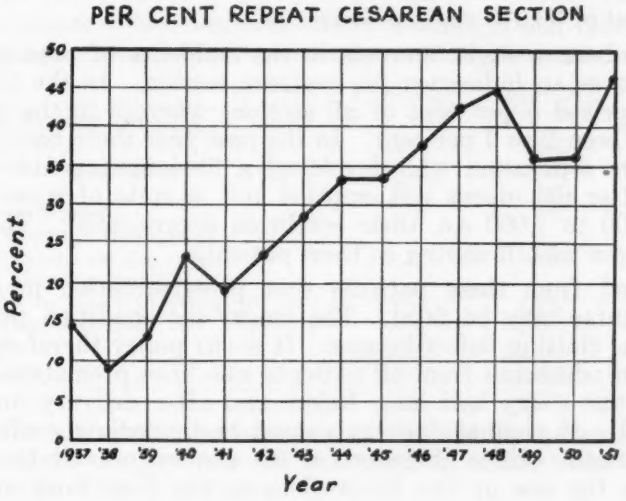

Fig. 2.

At Flushing Hospital, although regulations pertaining to cesarean section are rigid, consultation is not required for elective repeat section. Since 85 per cent of the deliveries are in private patients and since most of the staff do repeat sections in their private patients, this acccounts for our high incidence of repeat sections. However, not all of the operators routinely do repeat sections. Some allow a trial of labor, under proper conditions, in a patient who previously had a vaginal delivery and then had a section.

Another factor brought out by this survey is that up to 1947 approximately 80 per cent of all sections were of the classical type. Because of the greater danger of rupture of the classical scar in contrast to the transverse lower segment scar, repeat sections were performed in these patients. Since 1947 the number of low flap operations has risen to 63 per cent and the classical operation has dropped to 37 per cent. It may be that more vaginal deliveries may be attempted in place of repeat sections.

Hemorrhage.—

At the present time hemorrhage occupies third place, after repeat section and contracted pelvis and mechanical dystocia, as the indication for cesarean section. The incidence of placenta previa has remained about 7 per cent over the past 15 years at Flushing Hospital. In other clinics, placenta previa com-

prises 5 to 27 per cent of the indications for cesarean section.[6, 13, 22, 23, 24] In the treatment of placenta previa, section is employed in from 14 to 75 per cent of cases in various clinics, depending on whether expectant treatment is carried out.[5, 25] Johnson reported no maternal mortality in 79 cases of placenta previa, in 42 of which section was employed and in 37 of which treatment was conservative. Furthermore, the fetal mortality was average in cesarean section deliveries and lowest in conservative vaginal deliveries.[26]

It is our policy to attempt to carry the pregnancy in a bleeding patient as close to term as possible. If a central or complete placenta previa is found in a bleeding patient at term, a cesarean section is done. If any incomplete or partial placenta previa is diagnosed and bleeding is not excessive in a multigravida whose cervix is considered ripe for vaginal delivery, the membranes are ruptured and intravenous Pitocin is used if indicated. That maternal death may follow cesarean section for placenta previa is evidenced by the two deaths in our series of 1,303 sections, whereas only 1 death occurred from placenta previa in a total of 33,070 vaginal deliveries.

There has been a slight increase in the incidence of premature separation of the placenta as an indication for cesarean section. In the past 5 years this condition comprised 5 per cent of all sections whereas in the previous 5 year periods it had been 2 to 3 per cent. In the past year there have been 3 patients with premature separation who developed a fibrinogenopenia. Bleeding continued even after the uterus was emptied and in spite of massive blood transfusions of 5,000 to 7,000 c.c. their condition deteriorated. The use of intravenous fibrinogen was lifesaving in these patients.

We learned from these patients that procrastination in cases of severe abruptio placentae may be fatal. The longer the condition persists the more serious does the clotting defect become. It is our policy therefore to draw blood immediately on admission from all patients who have premature separation and to repeat the test every half hour before and after delivery until the clotting time is normal. If vaginal delivery cannot be immediately effected, we resort to cesarean section. Since fibrinogen is not generally available, we attempt to obtain it from the one or two institutions in the New York area where it is stored, and use fresh whole blood in large quantities to control the bleeding and the clotting defect until the fibrinogen is available. Cesarean hysterectomy is not the answer to this type of bleeding seen in premature separation, for bleeding continues from the skin and in the abdominal cavity even after removal of the uterus.

Intercurrent Disease.—

From 1937 to 1941 heart disease was the indication in 5 per cent of all cesarean sections. From 1941 to 1951 cesarean section for heart disease comprised less than 1 per cent of all sections. The fact that we no longer do sections for heart disease unless an obstetrical indication exists has greatly reduced this condition as an indication.

Tuberculosis as an indication for section has decreased from 2 per cent in 1937 to 1941 to zero from 1947 to 1951 in spite of the fact that more patients with pulmonary tuberculosis have been delivered at the hospital in the past 5 years. At present we do not resort to cesarean section for pulmonary tuberculosis except to avoid a prolonged, severe labor in a patient with an active or unstable tuberculous lesion.

Miscellaneous Indications.—

Among the miscellaneous indications, cesarean sections have been performed because of previous extensive vaginal plastic operations, prolapsed cord, cervical dystocia, previous stillbirths, uterine inertia, fetal distress, and the

fact that the patient is an elderly primigravida. In the last 2 years, 5 sections were done for fetal distress, more than were done over the previous 10 years. We believe that the early use of Pitocin will reduce the incidence of uterine inertia as an indication for cesarean section. Perhaps such indications as previous stillbirth, cervical dystocia, or elderly primigravida are occasionally tenuous. However, when several of these conditions exist in the same patient, cesarean section is frequently done.

Summary of Indications.—

In Table IV we have tabulated the indications for cesarean section and compared the incidence in the past 5 years to that of the previous 10 year period.

There has been a total decrease of 18 per cent in cesarean sections in the past 5 years compared to the previous 10 year period in the following conditions: contracted pelvis 8 per cent, cephalopelvic disproportion 4 per cent, toxemias 3 per cent, intercurrent disease 3 per cent.

TABLE IV. COMPARISON OF INDICATIONS IN PER CENT BETWEEN 1937-1946 AND 1947-1951

	1937-1946	1947-1951	DIFFERENCE IN LAST 5 YEARS
A. Conditions Showing Decrease.—			
Contracted pelvis	22%	13%	−8%
Cephalopelvic disproportion	19%	15%	−4%
Toxemia	8%	5%	−3%
Intercurrent disease	4%	1%	−3%
B. Condition Showing Increase.—			
Previous cesarean section	24%	41%	+17%
C. Conditions Showing No Change.—			
Dystocia due to faulty presentation	3.0%	3.4%	
Dystocia due to tumor	2.7%	2.0%	
Hemorrhage	10.0%	12.0%	
Miscellaneous	4.0%	5.0%	

Previous cesarean section accounted for a 17 per cent increase in the past 5 years compared to the previous 10 year period, thus almost nullifying the decrease observed in other indications.

There was no change in the percentage of cesarean sections for dystocia due to faulty presentation and tumors, hemorrhage, and miscellaneous indications. The slight increase in sections for premature separation in the past 5 years was not apparent in the hemorrhage cases because of the slight decrease in sections done for placenta previa.

The total incidence of cesarean sections over the past 15 years has remained between 3 and 4 per cent. It would appear that any further rise will come in the repeat cesarean group, which has been rising steadily and may be expected to rise further unless the policy, "once a section, always a section," is altered.

Summary

Although the trend in the recent literature is toward an increase in the incidence of cesarean section, mainly due to the addition of new indications, we have found a slight decrease in our section incidence in the last 5 years. Such indications as contracted pelvis, cephalopelvic disproportion, toxemia, and intercurrent disease showed a total decrease of 18 per cent in the past 5 years. We believe that this has resulted from more careful evaluation of our indications and from compulsory consultation by 2 qualified obstetricians before section is done. A thorough discussion of the indications for each section at the weekly staff conferences has further tended to reduce sections done for tenuous indications.

Operations performed for the indication previous section were increased by 17 per cent in the past 5 years. It may be that the increasing number of low cervical sections may be a factor in permitting more patients to deliver vaginally rather than performing repeat sections.

Such indications as dystocia due to faulty presentation or tumors, hemorrhage, and miscellaneous indications have shown no change in their incidence of section over the past 15 years. It is our belief that the judicious use of intravenous Pitocin has resulted in vaginal deliveries in many patients who previously might have come to section. We have found it extremely useful in patients with uterine inertia and in patients with hemorrhage where conditions for vaginal delivery exist but where delivery must be brought about rapidly. We have also noted a tendency to attempt induction with Pitocin in toxemic patients in whom we previously might have thought that labor could not be induced. Even when the Pitocin induction was not successful on the first attempt it usually resulted in vaginal delivery on a subsequent attempt the following day. We have also used Pitocin in patients in whom the question of slight cephalopelvic disproportion existed and in whom we felt an adequate trial of labor was indicated. With the more forceful uterine contractions produced by Pitocin, we have been able to evaluate such a patient within one to two hours as to the possibility of vaginal delivery. We have noted no untoward effects from this procedure and have frequently saved the patient from an unnecessary section.

Conclusions

1. The incidence of cesarean section at Flushing Hospital in the past 5 years was 3.4 per cent. This is less than the incidence in the previous 10 year period.

2. The factors that tend to promote expansion of cesarean section are discussed.

3. The following indications have shown an 18 per cent decrease in the past 5 years: contracted pelvis, cephalopelvic disproportion, toxemia, and intercurrent disease.

4. Previous section accounted for a 17 per cent increase in the past 15 years.

5. There was no change in the incidence of cesarean section for the following conditions: dystocia due to faulty presentation or tumor, hemorrhage, and miscellaneous causes.

6. The factors that tended to decrease cesarean sections were: (A) Compulsory consultation by 2 qualified obstetricians before section is performed; (B) staff conference reviews of indications for each section; (C) the judicious use of intravenous Pitocin to effect vaginal delivery.

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A STUDY OF THE MANAGEMENT OF PREGNANCIES SUBSEQUENT TO CESAREAN SECTION

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THE management of the parturient patient who has had a previous cesarean section is a problem with which we are being confronted more than ever before. With the section rate of recent periods varying from 2 to 6 per cent, we are meeting this situation in about 1.5 per cent of our obstetrical patients. The seemingly ever widening indications for section appear to give little hope that this percentage can be decreased, and from this group has arisen one of the most controversial subjects in the field of obstetrics.

When an obstetrical patient registers for our Clinic, a complete obstetrical history is obtained. In the event of a previous section, an attempt is made to evaluate that pregnancy as to the indication for section, the type of section, duration of labor, size of the infant, and any postpartum complications. The pelvis is evaluated, and should the previous indication be for cephalopelvic disproportion, x-ray pelvimetry is made at approximately eight and one-half months' duration of pregnancy; if indicated this should be repeated during labor. The scar should be examined periodically during the pregnancy for any palpable defects, and signs of impending difficulties necessitate admittance to the hospital. We section all patients showing x-ray or clinical evidence of definite disproportion, those with palpable defects and tenderness of the uterine scar, and those in labor who show suspicious signs of threatened rupture of the uterus. In the absence of such contraindications, we desire and attempt vaginal delivery; the patient is watched carefully during labor, with blood available, and with the ever present possibility in mind that interruption may become rapidly indicated.

It must be appreciated that the rupture of a uterus through an old cesarean section scar does not hold the catastrophic significance of the other varieties. The comparative avascularity of the scar usually prevents a rapid demise of the patient, and it is not at all unusual upon opening the abdomen to discover only minute amounts of blood to be present. This applies particularly to the scar of a low cervical section, for here we seldom note the explosive type of rupture which sometimes occurs in the classical scar. It is on this basis that we explain a much lower mortality rate, both maternal and fetal, following the low cervical scar rupture. The possibility of rupture in labor is by no means to be disdained, but neither is it to be viewed with abject terror.

Almost all authors quote a higher incidence of ruptures in classical scars than in low cervical scars. Two or more factors are probably responsible. The classical line of incision is through the active musculature of the uterus, and is

thoroughly jolted and agitated by the physiological contraction and relaxation during the puerperium. Thus, healing does not occur in an ideal environment. In the low cervical scar this tendency is not present to such a large degree, and superior scars tend to result. Second, the bladder flap of peritoneum in the low cervical section acts as an added barrier to the spread of infection. For these reasons, the classical cesarean section is becoming outmoded and used only in times of emergency when the matter of several minutes is of grave significance.

The proponents of "once a section, always a section" point out that there is no way to evaluate the strength of a uterine scar; therefore there is no reliable way of determining which patients will go through labor safely. Of course, we do not dispute the statement as such. However, we justifiably assume that everyone will section patients in whom the indication for the previous section is still present, and also patients in whom any suspicious signs or symptoms of a defective scar or impending rupture are noted or appear during labor. This study indicates that with modern medical care, the remainder who are allowed to attempt vaginal delivery will exhibit a lower maternal and fetal mortality rate than would occur if these patients were automatically sectioned. Thus, we feel this statement by the section advocates is true as literally stated, but it is misleading in its implications.

If an individual follows the teaching of elective repeat section, the problem of prematurity assumes an important role. There is, as yet, no known means of assuring the correct estimation of fetal size, and anyone doing very many elective sections will not too seldom be surprised by the delivery of an unsuspected premature infant. Wilson, in a report covering the years 1944 to 1950, reports over 10 per cent prematurity in 132 consecutive elective repeat sections; prematurity was considered to be infants weighing 5½ pounds and less. Also worthy of consideration is the belief that the premature infant of cesarean section does not do as well in the neonatal period as the vaginally delivered premature infant.

Only in the past several years have reports been published which discuss cases of ruptured uterus in the era of widespread blood banks, antibiotics, better surgical techinque, and better anesthesia. Previous mortality rates have been from cases prior to these eras, for many years are needed to accumulate a significant number of cases. Thus mortality rates since 1930 show a marked improvement and may necessitate a revamping of many physicians' attitudes, for they must now compare these new and improved mortality rates with their own.

Here, at the University of Texas, we continue to believe that a section for a temporary condition does not necessarily justify a section in each succeeding pregnancy. The decision on a problem of this kind cannot be decided on the basis of the experience of any one individual. One unfortunate experience will occasionally shape an individual's policy thereafter, and he will quote this experience in defense of his policy while neglecting to take note of the conclusions which may be drawn logically from the study of several thousand cases.

The material and percentages presented here were gathered in this manner. All articles published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY which concerned cesarean section, ruptured uterus, and labor following previous cesarean section for the past two and one-half years were reviewed. The major references from which each paper quotes were reviewed. It was felt that only by approaching it in this manner, and reviewing all articles regardless of the viewpoint of the author, could an undistorted conclusion be presented. Statistics from our University Hospital regarding ruptured uterus were purposely avoided, for our relatively small series would contribute little to the over-all picture. The desire was to give a presentation of statistics in the literature which are readily available to all.

In reviewing these articles some difficulty was experienced at times, for occasionally in presenting his study the author neglected to include vital information. Some authors occasionally use corrected statistics from their own point of view, and uncorrected statistics from the opposing opinions. A rather common error is the author's use of his own present-day mortality rates, while quoting the opposing mortality rates from twenty or thirty years ago. The purpose of these statements is not for derogation, but entirely to emphasize that careful scrutiny is necessary.

Material

In the review of 21,151 sections done during the years 1931 to 1950 there were 396 maternal deaths. This establishes a maternal mortality rate of 1.9 per cent. Only five of the articles reviewed furnished sufficient details regarding fetal mortality to establish a fetal mortality rate. There were 1,196 fetal deaths in the 14,006 sections reported by these five articles, or a fetal mortality rate of 8.5 per cent.

TABLE I. MATERNAL AND FETAL MORTALITY IN 21,151 CESAREAN SECTIONS 1931 TO 1950

AUTHOR	YEARS INVOLVED	NO. OF SECTIONS	MAT. MORT.	FETAL MORT.	% MAT. MORT.	% FETAL MORT.
Irving	1934–1943	1,887	24	120		
Manahan	1932–1941	750	13	?		
De Normandie	1937–1941	11,030	273	986		
Hennessy	1932–1946	536	10	52		
Dieckman	1931–1949	2,871	12	?		
Barney	1931–1941	1,317	24	?		
Geiger	1938–1947	266	4	19		
Douglas	1932–1948	1,622	16	?		
Verch	1933–1937	287	8	19		
Schmitz	1931–1950	585	12	?		
Total		21,151	396	1,196*	1.9%	8.5%*

*Based on the five reports involving 14,006 sections in which the fetal mortality was definitely stated.

In the review of 6,314 sections done during the years 1940 to 1951 there were thirteen maternal deaths. This establishes a maternal mortality rate of 0.21 per cent. Only eight of the articles reviewed furnished sufficient details regarding fetal mortality to establish a fetal mortality rate. There were 288 fetal deaths in the 5,123 sections reported by these eight articles, or a fetal mor-

tality rate of 5.6 per cent. The improvement in mortality rates of the past decade over the summation of the past two decades is noted. The reason for such a comparison will be pointed out later.

It was not possible to obtain a large enough series of cases of elective cesarean section to determine a dependable mortality rate. It is desirable to ascertain this rate for the sake of comparison. It was felt that this rate could be determined by examining the causes of death in each article, and correcting for each case in which the cause of death was present prior to surgery. In other words, in order to be considered as a mortality the death must be directly attributable to the surgery, or a result of the surgery, or the anesthesia of the surgery.

TABLE II. MATERNAL AND FETAL MORTALITY IN CESAREAN SECTIONS, GROSS AND CORRECTED* 1940 TO 1951

AUTHOR	YR. OF CASES	NO. OF SECT.	GROSS				CORRECTED*			
			MAT. MOR.	FET. MOR.	% MAT. MOR.	% FET. MOR.	MAT. MOR.	FET. MOR.	% MAT. MOR.	% FET. MOR.
Dieckman	1942-49	1,371	2	81			2	?		
Cody	1941-50	231	2	35			0	?		
Conti	1940-49	118	0	16			0	?		
McLean	1945-49	1,192	0	63			0	?		
D'Esopo	1942-47	1,000	1	37			0	3		
Douglas	1943-48	770	3	?			0	?		
Verch	1943-47	560	0	23			0	?		
Zarou	1944-51	400	1	20			0	2		
Eames	1940-51	421	1	?			0	?		
Kistner	1940-49	251	3	13			3	?		
		6,314	13	288	0.21%	5.6%	5		0.08%	
(Kistner)†		(57)		(4)				2		
(Wilson)†	1944-50	(331)		(11)				2		
		1,788‡						9‡		0.5%‡

*Corrected so the mortality rate approximates the risk in elective repeat cesarean section.

†Cases composed of elective repeat cesarean sections only.

‡Based on the four reports covering 1,788 sections in which sufficient details are available to permit proper corrections for fetal deaths.

Thus I have corrected the statistics in cesarean section for the years 1940 to 1951 so the remaining mortality is comparable to the risk of an elective section. In these 6,314 sections there were thirteen maternal deaths. Eight of these deaths are felt to be deductible from the gross number, the cause of death having been present prior to the section. These causes were: (1) adenocarcinoma of the liver, (2) acute intestinal obstruction, (3) neurogenic sarcoma in the pelvis, (4) fulminating bilateral renal cortical necrosis, (5) acute poliomyelitis, (6) hypertension and decompensation, (7) post mortem section, and (8) postoperative recurrence of acute rheumatic fever. Five cases are not felt to be deductible and to be part of the inevitable risks accompanying any major surgical undertaking. These were: (1) in three cases death, due to anesthesia, (2) in two cases, death due to pulmonary embolism.

Following that conception we determine 5 maternal deaths in 6,314 sections, or a corrected maternal mortality rate of 0.08 per cent. Only four of the articles reviewed furnished adequate details regarding fetal death to permit the establishment of a fetal mortality rate by the criteria which we have assumed.

These four articles concern 1,788 sections and report 72 fetal deaths. Only nine of these fetal deaths are felt to be attributable to the surgery, thus the corrected fetal mortality rate is 0.5 per cent.

These maternal and fetal mortality rates, corrected to the elective cesarean section level, are almost exactly the same as those mentioned by Dieckmann. This corrected rate must, in fairness, be used in the comparison of the two opposing concepts of management, for the cases of "once a section, always a section" are elective and theoretically free from extraneous factors as antepartum hemorrhage, toxemias, and so on.

TABLE III. DURATION OF PREGNANCY AT TIME OF UTERINE RUPTURE

AUTHOR	NO. PRIOR TO 37 WK.	NO. OF REMAINING RUPTURES	
		NO.	DURATION STATED IN ARTICLE
Delfs	1	5	36-39 wk.
Bill	1	12	At or near term
Parker	3	4	36-39 wk.
Watt	2	3	36-40 wk.
Brierton	5	21	36-40 wk.
Beacham	7	15	36-40 wk.
Totals	19	60	
Per cent	24%	76%	

In this review it is found that 24 per cent of the ruptures occur previous to the thirty-seventh week of pregnancy; thus one-fourth of the patients experience rupture before the advocates of repeat section would have undertaken any active therapy. This approximates the percentage determined by La Mariana in 1932, and is a large corrective factor which is often neglected.

TABLE IV. INCIDENCE OF RUPTURED UTERUS, SUBSEQUENT TO CESAREAN SECTION, BY AUTHORS FAVORING VAGINAL DELIVERY

YEARS COVERED BY CASES	WILSON 1944-50	DELFS 1900-44	DUCKERING 1932-43	COSGROVE 1931-50	SCHMITZ† 1931-50	TOTAL	INCID.
Number of patients	498	624	445	500	190		
Number of classical scars	124	604*	169	5	?	902	
Number of low cervical scars	224	20*	141	495	?	880	
Number of ruptures					6		
Classical scar ruptures	5	10	3	5	?	23	2.6%
Low cervical scar ruptures	2	0	2	7	?	11	1.3%

Note: In the series by Wilson and by Duckering, there were 150 and 135 scars, respectively, of other and unknown types.

*Author states "almost all" were classical scars. Arbitrary assumption of twenty low cervical scars.

†Not included in totals as author made no statement as to the number of classical or low cervical scars in series.

In order to determine the incidence of ruptured uterus in trial vaginal delivery we must turn to authors who favor this method of treatment, for only they have series to report. In 902 cases of classical scars were 23 ruptures, or an incidence of 2.6 per cent. In 880 cases of low cervical scars there were 11 ruptures, or an incidence of 1.3 per cent.

TABLE V. INCIDENCE OF RUPTURE OF UTERUS OCCURRING IN "TRIAL VAGINAL DELIVERY"

	CLASSICAL SCARS	LOW CERVICAL SCARS
Total incidence of ruptures	2.6%	1.3%
24% of ruptures occur prior to thirty-seventh week of pregnancy		
	therefore,	therefore,
Practical incidence of ruptures	2.0%	1.0%

I believe that all will agree that the patients who spontaneously rupture prior to the thirty-seventh week of pregnancy represent a group which, for practical purposes, neither concept of management will adequately control. As this group represents 24 per cent of the patients, there remains only 76 per cent who are a problem of management. Since there is a total incidence of rupture of 2.6 per cent in patients in trial vaginal delivery with classical scars, and we may expect 24 per cent of our ruptures to occur before the thirty-seventh week of pregnancy, there is only an incidence of 2.0 per cent from a practical point of view. In like manner we determine the practical incidence of rupture in low cervical scars to be 1.0 per cent.

TABLE VI. MATERNAL AND FETAL MORTALITY IN RUPTURED UTERUS SUBSEQUENT TO CESAREAN SECTION
1931 TO 1950

YEARS COVERED BY CASES	WILSON 1932-50	PARKER 1932-49	BRIERTON 1932-46	COSGROVE 1931-50	SCHMITZ 1931-50	TOTALS	PER CENT
Number of ruptures	15	7	26	12	6	66	
Number with classical scars	11	7	19	5	2	44†	
Number with low cervical scars	4	0	7	7	3	21†	
Maternal mortality							
Classical scar ruptures	0	0	1	0	0	1	2.3%
Low cervical scar ruptures	0	–	0	0	0	0	0%
Fetal mortality			12				
Classical scar ruptures	7	5	?	4	2	18	72%
Low cervical scar ruptures	1*	–	?	0	0	1*	7%

*Duckering reports this case of fetal mortality following a low cervical rupture in the same institution in 1932.

†Totals apply only to maternal mortality. Brierton furnishes no information to permit use of his statistics for fetal mortality.

The maternal mortality rate following rupture of a cesarean section scar has been quoted widely as being approximately 14 per cent. However, take note of these series reporting cases since 1931, since the advent of a more modern medical era. In forty-four ruptured classical scars there was only one maternal death, a maternal mortality rate of 2.3 per cent. In twenty-one ruptured low cervical scars there were no maternal deaths.

It is fully realized that these statistics are from institutions which are equipped with house staff and facilities to care for any possible surgical

emergency. However it reveals a marked improvement and shows what can be accomplished in a good institution.

One article furnished insufficient information to permit its inclusion in the determination of the fetal mortality rate. In the remaining twenty-five ruptured classical scars there were eighteen fetal deaths, or a fetal mortality rate of 72 per cent. In the remaining fourteen ruptured low cervical scars there was one fetal death, or a fetal mortality rate of 7 per cent.

TABLE VII. MATERNAL AND FETAL MORTALITY IN RUPTURED CLASSICAL SCARS IN "TRIAL VAGINAL DELIVERY" 1931 TO 1950

	MATERNAL	FETAL
Practical incidence of rupture	2.0%	2.0%
Mortality in rupture	2.3%	72.0%
Therefore		
Incidence of mortality	0.05%	1.4%

The previously determined practical incidence of rupture of classical scars is 2.0 per cent. We have just determined the maternal mortality rate in rupture to be 2.3 per cent. Therefore, if we use trial vaginal delivery the incidence of maternal mortality we may expect is 2.3 per cent of 2.0 per cent, or 0.05 per cent. This is roughly one-half the maternal mortality rate following routine section. Fetal mortality as derived in like manner is 1.4 per cent, which is a little less than three times that of routine section.

TABLE VIII. MATERNAL AND FETAL MORTALITY IN RUPTURED LOW CERVICAL SCARS IN "TRIAL VAGINAL DELIVERY" 1931 TO 1950

	MATERNAL	FETAL
Practical incidence of rupture	1.0%	1.0%
Mortality in rupture	1.0%	7.0%
Therefore		
Incidence of mortality	0.01%	0.07%

The low cervical scar demonstrates much better results. The previously determined practical incidence of rupture is only 1.0 per cent. The 1 per cent maternal mortality rate given here is a theorizing assumption for, in the articles reviewed, there were no maternal deaths noted following rupture of a low cervical scar. To avoid criticism of the assumption of the low mortality rate of 1 per cent, may it be pointed out that the mortality rate in ruptured classical scars is only 2.3 per cent, and that the sequence of events in the low cervical rupture is of a much subdued nature. Thus 1 per cent of 1.0 per cent, or 0.01

TABLE IX. COMPARISON OF MORTALITY RATES IN "ONCE A SECTION, ALWAYS A SECTION" AND "TRIAL VAGINAL DELIVERY"

	MATERNAL	FETAL
Section	0.08%	0.5%
Vaginal delivery		
Classical scar	0.05%	1.4%
Low cervical scar	0.01%	0.07%

per cent, is the true incidence of maternal mortality occurring from ruptured low cervical scars in those who are thought to be acceptable risks for vaginal delivery. This is only one-eighth of the mortality which would occur should this group of patients be routinely sectioned. The fetal mortality in like manner is 0.07 per cent, or one-seventh of the mortality which would occur with routine section.

Summary

In reviewing these articles I have endeavored to present all relevant material and the numbers and percentages without distortion. Articles were taken consecutively, over a fixed period of time, in a fixed reliable publication, and without consideration as to the belief of the authors. This, I believe, is the best approach if we are to solve such questions.

The final results of this study are, more or less, two opposing rates of mortality. The results indicate that "once a section, always a section" does not give the superior results which its advocates believe, for they have not compared their results with present-day mortality rates in trial vaginal delivery, nor do they take into account a corrective factor which has been mentioned. Another point worthy of note is that the mortality rates for cesarean section used here are from cases since 1940, since the advent of penicillin and other antibiotics. The abrupt drop in mortality as we move into the decade 1940 to 1950 has been demonstrated in the statistics concerning cesarean section. At least one-half the ruptures in this series occurred in the decade 1930 to 1940, so there is every justification to believe that when series involving the truly modern medical era become available, the results will be still further in favor of trial vaginal delivery. The role of infection in the production of inferior scars is well known, and the widespread use of antibiotics should further decrease the incidence of rupture. Also the ever increasing use of the low cervical cesarean section over the classical cesarean section will steadily improve the outlook for vaginal delivery in acceptable cases.

It is felt that the statistics from low cervical scars speak for themselves, and lend less room for debate. In the classical scars we note a situation in which one concept offers less risk to the mother, while the opposite concept favors the infant. It becomes a matter of which we desire to protect to the greatest degree. Most of us will choose the mother as our primary interest, thereby indicating, we believe, trial vaginal delivery as the choice.

The question as to proper management will no doubt be studied for some years before the final answer is determined. The factor most accountable for such a delayed decision is the small incidence of ruptures and consequent delay in the collection of a large series of cases.

We continue to practice trial vaginal delivery, and this review of literature indicates it to be the management of choice.

Conclusions

1. Vaginal delivery following a previous cesarean section for a temporary condition is the management of choice, unless signs or symptoms of impending rupture, faulty scar, or other complicating pathology is present.

2. In patients acceptable for vaginal delivery, as defined above:
   a. Classical scars
      (1) Elective cesarean section maternal mortality rate is one and a half times that of vaginal delivery.
      (2) Elective cesarean section fetal mortality rate is one-third that of vaginal delivery.
   b. Low cervical scars
      (1) Elective cesarean section maternal mortality rate is eight times that of vaginal delivery.
      (2) Elective cesarean section fetal mortality rate is seven times that of vaginal delivery.

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A STUDY OF CESAREAN SECTION AT EVANSTON HOSPITAL FROM 1930 TO 1950*

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CESAREAN section is a useful method of managing certain serious complications of pregnancy and labor. However, since with the passage of time our attitudes toward this procedure have gradually changed, it has seemed desirable to undertake the present study. This, therefore, is a statistical analysis of cesarean sections performed at Evanston Hospital during the years 1930 to 1950.

The Evanston Hospital is a general hospital of 337 beds in which the work is largely private. The greatest share of the work of this hospital is performed by the members of the attending staff who are also members of the faculty of the Northwestern University Medical School.

Between the years 1930 and 1950, 21,612 patients were delivered. Of these, 896, or 4.14 per cent, were delivered by cesarean section.

Results

Incidence.—The incidence of cesarean section in this hospital as indicated in Table I has not varied significantly during the past twenty years and compares favorably with the published data of other institutions, many of which report on ward or service patients. No attempt has been made to separate private and ward patients in our study, since the latter actually comprise an extremely small number of cases. The yearly incidence of cesarean section at the Evanston Hospital as shown in Table II has been surprisingly constant.

TABLE I. INCIDENCE OF CESAREAN SECTION, 1941-1945

Margaret Hague Maternity	2.6%
Chicago Lying-in	4.3%
Boston Lying-in	3.5%
Johns Hopkins	4.8%
Cleveland Maternity	5.5%
University of Pennsylvania	7.0%
Stanford University	6.2%
New York Lying-In	3.2%
Average	4.7%
Evanston Hospital (1930-1939)	4.20%
Evanston Hospital (1940-1949)	4.08%

Maternal Mortality.—Comparative mortality rates in cesarean section are shown in Table III.[1] The seven fatal cases which occurred are summarized in Table IV. The last 441 cesarean sections in this series were performed without a death.

Fetal Mortality.—The fetal mortality rates in cesarean section as compared to these in vaginal delivery are presented in Table IV*B*. In our series,

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there is an uncorrected fetal mortality rate of 7.3 per cent in cesarean section and an uncorrected fetal mortality rate of 3.0 per cent for vaginal delivery.

Morbidity.—The over-all morbidity (temperature of 100.4° F. on any two postpartum days from the second to the eleventh day) was 22.4 per cent. The most common causes of morbidity were endometritis, wound infection, and upper respiratory infection, in the order named.

TABLE II. INCIDENCE AT EVANSTON HOSPITAL

YEAR	C. S.	DEL.	INCIDENCE (%)
1930-1939.—			
1930	46	977	4.72
1931	29	839	3.46
1932	36	721	4.98
1933	42	675	6.21
1934	32	764	4.18
1935	30	866	3.46
1936	37	806	4.58
1937	29	925	3.13
1938	31	891	3.47
1939	35	920	3.81
1940-1949.—			
1940	36	955	3.76
1941	35	1,017	3.45
1942	37	1,231	3.0
1943	47	1,236	3.8
1944	56	1,278	4.38
1945	62	1,241	4.88
1946	67	1,550	4.32
1947	72	1,652	4.35
1948	66	1,496	4.42
1949	71	1,572	4.52
Average			4.14

TABLE III. MATERNAL MORTALITY

	NUMBER	INCIDENCE (PER CENT)	MORTALITY (PER CENT)
Boston Lying-in, 1941-1945	522	3.5	0.57
Chicago Lying-in, 1941-1945	616	4.3	0.32
Cleveland Maternity, 1941-1945	1128	5.5	0.62
Johns Hopkins, 1941-1945	455	4.8	0.21
Margaret Hague, 1941-1945	902	2.6	0.66
New York Lying-In, 1941-1945	535	3.2	0.37
University of Pennsylvania, 1941-1945	840	7.0	0.35
Stanford University, 1941-1945	429	6.2	0.00
Toronto General, 1940-1949	1710	4.4	1.28
Cincinnati General, 1940-1949	251	1.0	1.1
Average		4.3	0.55
Evanston Hospital, 1930-1939	347	4.2	1.44
Evanston Hospital, 1940-1949	549	4.08	0.34

Type of Operation.—The procedures employed are shown in Table V. The majority of low cervical cesarean sections were performed according to an accepted technique,[2] employing a longitudinal uterine incision. In recent years, increasing use has been made of the transverse uterine incision.

Indications.—The recorded indications are listed in Table VI. Perusal of this list suggests that it might be possible to reduce our incidence of cesarean section. The listed indications, however, are primary ones, and in those which might appear somewhat dubious there were generally other secondary indications which strengthened the desirability of abdominal delivery.

TABLE IV*A*. ANALYSIS OF MATERNAL DEATHS

YEAR	AGE	PARA	PREVIOUS CESAREAN SECTION	INDICATION	CAUSE OF DEATH
1931	38	i	0	Toxemia (mitral lesion)	Pulmonary embolism
1932	26	i	0	Mitral stenosis (with regurgitation)	Endocarditis (85th day post partum), *Streptococcus viridans*
1934	33	i	0	Test of labor	Postpartum hemorrhage and shock
1935	44	iv	0	Acute intestinal obstruction and toxemia	Peritonitis due to spontaneous perforation of cecostomy due to cancer of colon
1935	40	iii	2	Repeat cesarean sections	Acute peritonitis, paralytic ileus
1941	21	i	0	Toxemia	Uremia due to acute glomerular nephritis
1942	22	i	0	Toxemia	Hepatitis

TABLE IV*B*. FETAL MORTALITY, GROSS

YEAR	VAGINAL DELIVERY (PER CENT)	CESAREAN SECTION (PER CENT)
1930	4.2	2.1
1931	3.2	.0
1932	2.9	.0
1933	3.4	4.7
1934	2.5	15.6
1935	3.8	6.6
1936	3.3	8.1
1937	2.6	3.4
1938	3.7	22.0
1939	2.2	8.6
1940	3.2	5.5
1941	1.8	5.7
1942	2.8	16.2
1943	3.4	8.5
1944	2.9	7.1
1945	2.5	4.8
1946	3.8	5.9
1947	3.1	6.9
1948	2.7	6.0
1949	3.0	11.2
Average	3.0	7.3

TABLE V. TYPE OF OPERATION

PROCEDURE EMPLOYED	NUMBER	PER CENT
Low cervical	869	96.88
Classical	20	2.34
Cesarean hysterectomy	7	0.78

Uterine inertia does not appear as a primary indication. Many of the patients with disproportion did have some degree of uterine inertia.

Labor and Membranes.—The data concerning labor and membranes are presented in Table VII. Labor was present in some degree in 23 per cent of all cases and the membranes were ruptured for varying lengths of time before section in 13.5 per cent of all cases.

Age and Parity.—Age and parity are presented in Table VIII. The majority of cesarean section patients fell into the 25 to 35 year age group which represents the period during which most of the pregnancies occurred. About twice as many patients were in the 35 to 39 year group as were in the younger

TABLE VI. INDICATIONS

	NO. OF CASES		PER CENT
Repeat		334	37.3
Disproportion		202	22.5
Toxemia		100	11.1
Placenta previa		74	8.3
Abruptio placentae		35	3.9
Heart disease		19	2.1
Tuberculosis		5	0.5
Diabetes		7	0.7
Nephritis		1	0.1
Myasthenia gravis		1	0.1
Retinitis pigmentosa		1	0.1
Renal calculi (large)		1	0.1
Pyelitis with anuria		1	0.1
Cervical dystocia		10	1.1
Fibroids		10	1.1
Ovarian mass		8	0.9
Breech		17	1.8
Transverse lie		4	0.4
Brow		1	0.1
Face		1	0.1
Twins		1	0.1
Bicornuate uterus		4	0.4
Pelvic fracture		4	0.4
Bilateral hip dislocation		1	0.1
Postmaturity*		2	0.2
Hydrocephalus		1	0.1
Prophylactic		51	5.7
Previous dystocia	26		2.9
Previous third degree laceration	6		0.7
Myomectomy	4		0.5
Elderly gravida i†	6		0.7
Pituitary tumor	1		0.1
Previously dead baby	2		0.2
Short cord	2		0.2
Cervical plastic	2		0.2
Erythroblastosis	1		0.1
Psychiatric reasons	1		0.1

*Postmaturity: infant weights
1. 3,170 grams
2. 3,720 grams.

†Elderly gravida i (37-47 years)—average age, 41.6 years.

TABLE VII. LABOR AND MEMBRANES

	NUMBER	PER CENT
Labor.—		
No labor	692	77.2
Less than 6 hours	48	5.4
6 to 11 hours	28	3.1
12 to 17 hours	48	5.4
18 to 23 hours	31	3.4
24 to 29 hours	27	3.0
30 hours and over	22	2.5
Membranes.—		
Intact	775	86.5
Ruptured:		
5 hours or less	46	5.2
6 to 9 hours	13	1.5
10 to 14 hours	20	2.3
15 to 19 hours	5	0.5
20 to 24 hours	15	1.7
25 to 29 hours	5	0.5
30 hours and over	12	1.3
Unknown	5	0.5

group of 20 to 24. Apparently no parity was exempt, although incidence of cesarean section was very low in those patients who had had many deliveries.

Anesthesia.—Inhalation anesthesia was used in 82.5 per cent of the cases, spinal in 11.9 per cent, and local in 5.6 per cent. There were no deaths ascribable to anesthesia nor were there any sequelae of consequence following spinal anesthesia. Currently, our preference is for spinal anesthesia unless there is some contraindication.

TABLE VIII. AGE AND PARITY

	NUMBER	INCIDENCE (PER CENT)
Age (years).—		
15-19	12	1.5
20-24	96	10.8
25-29	268	30.1
30-34	271	30.5
35-39	196	21.0
40-	53	6.1
Parity.—		
Gravida i	392	43.6
Gravida ii	337	37.7
Gravida iii	120	13.5
Gravida iv	30	3.3
Gravida v	11	1.2
Gravida vi	4	0.5
Gravida vii	2	0.2

Other Surgery.—Incidental surgery is listed in Table IX. Although no complete hysterectomies are listed prior to 1950, all cesarean hysterectomies performed since then have been of the complete type. This will undoubtedly constitute our preference in the future. Some type of sterilization procedure was done 206 times for an over-all incidence of 25 per cent. These 206 procedures account for 91.2 per cent of all other surgery. Sterilization is generally offered to the patient at the time of her third abdominal delivery.

TABLE IX. OTHER SURGERY

	NUMBER	PER CENT
Pomeroy resection	167	74.4
Madlener resection	26	11.3
Cornual resection	13	5.5
Subtotal hysterectomy	4	1.7
Myomectomy	4	1.7
Salpingo-oophorectomy (unilateral)	4	1.7
Oophorectomy (unilateral)	4	1.7
Appendectomy	1	0.4
Secondary repair of uterine scar	1	0.4
Salpingectomy (unilateral)	1	0.4
Umbilical herniorrhaphy	1	0.4
Cecostomy	1	0.4

Comment

On the basis of this study which represents the work of approximately ten obstetricians, certain generalizations can be drawn. During the years covered by this study, there were 21,612 deliveries, of which 896 were managed by abdominal delivery. This gives an incidence of 4.14 per cent or one section in every 24 deliveries. Although many clinics have reported an increase in the incidence of cesarean section, our year-by-year incidence is fairly constant.

There were 7 maternal deaths for an incidence of 0.84 per cent. All occurred in the group where the low cervical technique was employed. Our incidence approximates that of the national average of 0.61 per cent.[1] Two deaths were primarily from heart trouble, 2 were from toxemia, 2 were due to peritonitis, and 1 was caused by postpartum hemorrhage. Of the 7 deaths, 3 were considered unavoidable, making a corrected incidence of 0.45 per cent.

In our series there is an uncorrected perinatal mortality of 7.3 per cent. This compares favorably with a national average of 7.5 per cent uncorrected fetal mortality for cesarean section,[3] but is higher than our incidence of 3.0 per cent uncorrected mortality in vaginal deliveries for the same 20 year period. It is of interest to note that midforceps operations, according to "old style" definition, from 1940 to 1950, the last 10 years of the study, were attended by an uncorrected fetal mortality of 2.4 per cent. It was not possible to demonstrate a constant and definite relationship between the fetal mortality and the incidence of abdominal delivery.

We have been unable to show that a higher incidence of cesarean section would yield a lower fetal mortality.

There was a maternal morbidity of 22.4 per cent, the cause for which was undiagnosed in 95 cases. No correlation could be made between the time of rupture of the membranes and morbidity.

During the period of this study, 869, or 97 per cent, of the operations were done using the low cervical technique. Of the remaining cases, 20, or 2.5 per cent, were classical in type, and 7, or 0.85 per cent, were cesarean hysterectomies. The extraperitoneal techniques were absent from our series.

Among the indications there were 334 repeat sections for an incidence of 37.3 per cent. The fact that the greatest number of sections was in women who had previously been delivered by cesarean section indicates the great necessity for careful selection of patients for the primary operation. We believe that the advantages of repeat section outweigh possible uterine rupture.

Cephalopelvic disproportion ranked second in the indications with 202 cases, or 22.5 per cent. Most of these patients were given a trial of labor. In the latter years of this study, x-ray pelvimetry was used more frequently.

Toxemia ranked third as an indication. Statistics indicate the maternal mortality in eclampsia to be about 10 to 15 per cent.[4] The toxic patient is best treated medically but, should this fail, section is done if labor cannot be induced easily.

Placenta previa and abruptio placentae together constituted 12.2 per cent of the indications. Not all patients who had placenta previa or abruptio placentae were given blood transfusions. Each case was treated on its individual merits. There were 51 operations classed as prophylactic for an incidence of 5.7 per cent. This group was largely composed of those patients who had had previous dystocia. A study of the factors of labor, length of time of ruptured membranes, age, and parity has proved noncontributory.

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Discussion

DR. JAMES E. FITZGERALD.—It is interesting to note that in this series the authors have presented excellent results when cesarean section is used under the best of circumstances. It must be re-emphasized that these were all private patients under continuous prenatal supervision; that the indications were dictated and the surgery done by men who are active in University teaching. The incidence of cesarean section over a period of years remains static despite the increasing safety of the operation. This suggests that sound obstetric judgment has not been sacrificed to an easier way out for the staff.

Their gross and corrected fetal mortality is much higher than that in vaginal delivery. This, of course, is true in all reported series and is due in part to the high incidence of prematurity in cases of section because of maternal hemorrhage or toxemia. Nevertheless, this higher fetal mortality does suggest that cesarean section per se does not guarantee fetal survival.

It is of interest to note that spinal anesthesia is preferred at this time. With this I am wholly in accord. I am sure all of you realize that it is but a short time since spinal anesthesia in obstetrics was mentioned only to be condemned in our community.

There being practically no controversial points in this paper, one may be permitted to ask the authors for clarification on certain points.

1. Twenty-two and five-tenths per cent of their operations were done for disproportion. This is in line with textbook averages but seems rather high for the type of patient considered in their report. How many of these patients had a test of labor and what do the authors consider a test of labor?

2. Has x-ray pelvimetry, which they say has been increasingly utilized of late, increased their incidence of elective section?

I may be permitted to point out that of 896 cesarean sections, two were done for postmaturity, and rather normal-sized infants were delivered, yet no cesarean section was done because of contraction ring. Is this class of patients immune to such pathologic rings?

Last, 206 sterilizations were done, presumably on patients with previous section. The essayists said that a considerable number of these patients were over 35 years of age. Is it not possible that these patients, or many of them at least, would have been better served by hysterectomy at the time of the last cesarean section instead of merely tying the tubes? I want to remind you that out of 896 patients only 7 had cesarean hysterectomies.

DR. ZETTELMAN (Closing).—There has been no cesarean section for erythroblastosis fetalis. Pelvimetry has been done in increasing degree and usually it is possible, if anything, to decrease the incidence of cesarean section by pelvimetry.

Concerning constriction ring: In the first place, this analysis has been mainly from records and many of the old records had been photographed. It has been necessary to go back and review the photographic copies. It has been necessary and difficult for us to place ourselves in the place of the doctor who made the original diagnosis and did the section. All we can do is to read what he has on the record and try to follow the same line of thought. This has not been easy. Probably a trial of labor was given in many instances but it did not show on the record.

The use of cesarean hysterectomy for sterilization has not appeared in this series.

CONSTRICTION RING DYSTOCIA*

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DYSTOCIA due to a constriction ring can be a formidable complication in labor, and if not properly managed, may result in serious consequences to both mother and infant. This condition is due chiefly to a functional disturbance of the uterine muscle, and, as long as this disturbance persists, the uterus cannot empty itself. A review of 44 cases, collected from the Cook County and Mount Sinai Hospitals from the years 1947 to 1951, inclusive, demonstrates that we are not adequately aware of the possible presence of a constriction ring when the first or second stage of labor is prolonged. In many instances, its presence is recognized only after a traumatizing attempt to deliver the baby.

A constriction ring is an annular contraction which may occur at various levels of the uterus, i.e., in the upper uterine segment, at the junction of the upper and lower uterine segments, and at the "obstetric" internal os, or the external os of the cervix. It is most commonly found at or near the junction of the upper and lower uterine segments. It frequently causes dystocia in the presence of a normal cephalopelvic relationship and normal fetal presentation and position. The ring does not change position as labor progresses. It frequently forms over a depression in the infant's outline, as, for instance, around the fetal neck, but has also been found below the presenting part. It occurs in the first, second, and third stages of labor and, as White[1] has stated, even before there are signs that labor has started. It is associated with an incoordination of the uterine action so that the normal physiologic changes associated with the progress of labor are altered.

Rupture of the uterus due solely to the ring has never been demonstrated, but may occur from other complicating factors, such as misdirection of the presenting part, when high against the bony pelvis. The pressure of the fetal head against the uterine portion in contact with the bony structure may cause local ischemia and necrosis with subsequent rupture. Rudolph[2] described two types of constriction rings: (1) the reversible ring which relaxes under anesthesia, amyl nitrite, Adrenalin, papaverine, or Spasmalgin, and after incision or after death; (2) the irreversible ring which does not relax under anesthesia or drugs or even after death, as demonstrated in the cases of White,[3] Phillips,[4] Hannah and Massey,[5] Carson,[6] Michael,[7] and more recently of Louw.[8]

Etiology

A study of the literature and our observation of constriction ring dystocia for the past twenty years have not revealed any clear-cut predisposing factors. Rudolph[2] describes it as being due to a disturbance of the physiology

*Presented before the Chicago Gynecological Society, Nov. 21, 1952.

of the uterus in labor of unknown cause. Jeffcoate[9] is of the opinion that it is due to a persistent localized spasm of an annular area of uterine muscular wall, probably the result of incoordinate uterine action. Rucker[10] believes that it is due to a fatigue phenomenon. Age, parity, rupture of the bag of waters, malposition and malpresentation, bags and drugs are not of etiological importance. Intrauterine manipulation may be of some significance. A psychosomatic factor may play a role and is worth mentioning.

Frequency

Kennedy[11] states that the frequency of constriction ring dystocia is 0.26 per cent, or about one in four hundred labors, his statistics corresponding well with McKenzie's[12] of 0.25 per cent, Adams's[13] of 0.28 per cent, and ours of 0.23 per cent. Johnson[14] reports an incidence of 1.26 per cent and Rucker[15] an incidence of 1.67 per cent. Both of these figures seem to be rather high.

Diagnosis

A constriction ring should be suspected when labor fails to progress despite an apparently normal presentation and position. Rudolph made such a presumptive diagnosis in all cases of prolonged labors, a thought very worthy of consideration. With that thought in mind, one should look for any or all of the cardinal signs of a constriction ring. These signs are as follows:

In the First Stage: (1) A depression or groove may be felt or seen abdominally. (2) The cervix usually hangs loosely like a cuff, especially during a uterine contraction. (3) The head often is easily rocked in the pelvis.

In the Second Stage: (1) There is station recession during a uterine contraction. (2) The lower uterine segment and cervix are flaccid.

Fig. 1.—Depression on anterior abdominal wall, suggestive of an intrauterine ring at that level.

The absolute diagnosis is made by an intrauterine examination, at which time the ring can be palpated. However, a transverse extrauterine depression or furrow (to which we refer as a ring) early in labor, which is seen or palpated on the anterior abdominal wall, is suggestive of a constriction ring at that level (Fig. 1).

Prognosis

The prognosis depends upon a correct diagnosis and proper management. Prior to the introduction of the low cervical cesarean section and chemoantibiotic therapy, the maternal mortality was as high as 20 to 30 per cent. The fetal loss ranged from 40 to 80 per cent. As late as 1941, McGill[16] re-

ported a maternal mortality of 15 per cent and a fetal mortality of 46 per cent. Rudolph and Fields[17] reported a fetal mortality of 32 per cent, and a maternal mortality of 3.5 per cent. In 1946, H. Johnson[14] reported on 105 cases without a maternal mortality and only a 4.7 per cent fetal mortality. The most remarkable figures are those of Rucker.[18] In his last 54 cases of constriction ring, all mothers and infants survived, and none were delivered by cesarean section.

A review of the results in the series herewith reported, as compared with previous reports from the same institutions, reveals a greatly improved prognosis for the mother and infant (Table I). The fact that we did not have a maternal death does not mean that the condition has ceased to have its dangers for the mother. An early diagnosis was not made in most of these cases. The improvement in our results must be attributed to the fact that blood transfusions and antibiotics have enabled us to perform safely a lower uterine segment cesarean section in cases of prolonged labor in the presence of actual or potential infection.[19-20]

TABLE I. COMPARISON OF STATISTICS FROM THE SAME INSTITUTIONS

	NO. OF CASES	MATERNAL MORTALITY (%)	FETAL MORTALITY (%)	CORRECTED FETAL MORTALITY (%)	CESAREAN SECTIONS (%)
Rudolph up to 1935	21	9.5	24		0
Rudolph and Fields, 1936 to 1946	56	3.5	32		25
Fields, 1947 to 1951	44	0	11.6	6.8	75

Management

The management of a constriction ring dystocia is essentially the management of prolonged labor. However, if one keeps in mind that a constriction ring may be prolonging the labor, the first and second stages can be managed with more safety to the mother and baby.

The First Stage of Labor

Often a patient has premonitory pains of labor which may be severe, but which have no effect on the cervix and are therefore false labor. She becomes mentally disturbed and does not partake of food, and by the time she enters the hospital she is potentially exhausted. If this prodromal period rapidly blends into true labor, as evidenced by the onset of cervical dilatation and the labor terminates normally, the state of exhaustion will not become manifest. When at the end of eighteen hours of true labor the cervical dilatation is not complete, the cause of the failure of progress should be determined. At this time, a thorough examination should be made to determine whether or not the most severe type of uterine incoordination, a constriction ring, may be present. The abdomen is inspected and palpated for a depression or groove. A sterile vaginal examination should then be made to determine the condition of the cervix. If the cervix hangs loosely like a cuff, especially during a uterine contraction, and the head can be easily rocked in the pelvic cavity, both pathognomonic signs of a constriction ring, then the hand should be introduced into the uterine cavity. This can be accomplished with light anesthesia if the cervix has dilated to 4 cm. or more. In the majority of cases, a constriction ring can most certainly be palpated around the fetal neck.

If a constriction ring is found, the patient should be given general supportive treatment. The urine should be tested for acetone and, if positive, treat-

ment for acidosis should be instituted. The diet, liquid or soft, should be high in calories and rich in carbohydrates. If the patient is unable to take nourishment by mouth, intravenous glucose, 10 per cent solution, should be administered. Sedation in the form of antispasmodics, such as Spasmalgin, 1 ampule, with scopolamine should be given; the Spasmalgin may be repeated. After such treatment over a period of ten to twelve hours, the ring may relax and labor terminate either spontaneously or by outlet forceps. Until the cervix is completely dilated, active intervention via the vaginal route should be avoided. Manual dilatation of the cervix, or of the ring, although still advised by one author, is to be condemned as dangerous. If at the end of the period of conservative treatment the ring has not relaxed, as evidenced by the absence of further cervical dilatation, a cesarean section is the treatment of choice. A special point in technique should be emphasized in the performance of a cesarean section for constriction ring dystocia; namely, the use of a longitudinal incision in the uterine wall, in order that the original incision can be extended to include the ring if necessary.

Dührssen's incisions, in the presence of a constriction ring, should be mentioned only to be condemned. When incisions of the cervix are contemplated, it should be routine to do an intrauterine examination to rule out the presence of a constriction ring. Failure to recognize the presence of a constriction ring may result in irreparable fetal damage, and severe trauma to the maternal soft parts with shock, and even death.

The following case demonstrates the management of a first-stage constriction ring.

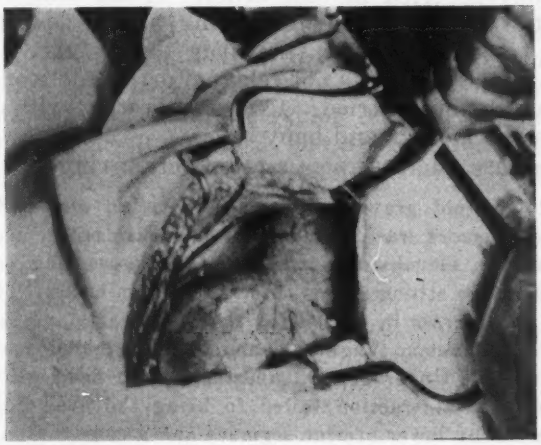

Fig. 2.—Depression seen and felt when the abdomen was opened in Case 1. To the left is the upper uterine segment and to the right is the lower uterine segment; note groove between them. This coincided with the intrauterine ring around the fetal neck.

Case 1.—A 20-year-old Negro gravida iii, para ii, whose due date was Dec. 8, 1951, entered Cook County Hospital on Dec. 3, 1951, in apparent labor. Examination revealed that the cervix was thick and closed, and that the presenting part was floating. Eighteen hours later, the cervix was effaced, and 5 cm. dilated. There was a cephalic presentation with station at –1, impressed to 0. The bag of waters was ruptured artificially to hasten labor. Two hours later, a depression was seen and felt three fingerbreadths below the umbilicus. The depression was accentuated during a contraction. Since a constriction ring was suspected a sterile vaginal examination was done. The cervix was found to be 5 cm. dilated, loose and hanging like a cuff with a cephalic presentation at –2 station. Intrauterine examination, under anesthesia, revealed a thick constriction ring between the head and the shoulders.

The patient was given papaverine, 2 grains, intravenously, magnesium sulfate, 10 c.c. of a 25 per cent solution intravenously, morphine sulfate, ⅙ grain subcutaneously. This had no effect on the ring; the cervical dilatation remaining unchanged. Therefore, eight hours after the medication, a cesarean section was performed.

At section, the lower uterine segment was ballooned out. A constriction ring was easily seen and palpated about the neck of the fetus (Fig. 2). A longitudinal incision was made in the uterine wall, including the ring, and a live baby easily delivered. The postoperative course was complicated only by a one-day temperature of 102.4° F. The baby was in good condition and weighed 6 pounds, 8 ounces. The mother and baby left the hospital on the ninth postoperative day.

The Second Stage of Labor

Usually, when the second stage of a normal labor is reached, true descent of the presenting part begins. If, after two hours in the second stage, the presenting part fails to descend despite adequate uterine contractions, the cause for the failure of progress should be sought. If the fetal head fails to descend during a uterine contraction, as pointed out by Gilliatt,[21] or even recedes very slightly, as emphasized by Pendleton,[22] one should suspect a constriction ring. An intrauterine examination makes the diagnosis with certainty.

While the obstetrician's fingers are in the uterus, amyl nitrite in doses of 1 to 6 perles may be administered by inhalation. If this fails to relax the ring, Adrenalin, 10 minims subcutaneously, papaverine, 1 grain intravenously, and magnesium sulphate, 10 c.c. of a 20 per cent solution intravenously, as advocated by Abarbanel,[23] may be tried in that order. If the ring relaxes with any of these drugs and the station of the presenting part is low, the forceps are applied and, before traction is begun, the drug that relaxed the ring in the test dose is repeated. If the ring does not relax, efforts to deliver the baby vaginally by any means should not be tried. Cesarean section will give a much better prognosis for both the mother and baby.

The following case demonstrates a constriction ring in the second stage.

CASE 2.*—A 26-year-old gravida ii, para i, with an uneventful pregnancy, whose estimated date of confinement was Feb. 9, 1948, entered Mount Sinai Hospital on Feb. 7, 1948, in labor. After an eleven-hour first stage, the presenting part was at station 0, the pains were moderately strong every three to four minutes. The patient was given sedation, and since no progress in descent of the head was made in the next four hours, she was prepared for delivery. Vaginal examination revealed a right occipitoposterior position, station 0 to +1. Under general anesthesia, the head was manually rotated to right occipitoanterior. Trial traction failed to bring the head down. Intrauterine examination revealed a flabby lower uterine segment and a constriction ring around the fetal neck. The patient was allowed to awaken and was put back to bed.

An hour later she was seen by a consultant, who confirmed the diagnosis of a constriction ring. She was placed under deep ether anesthesia and given 15 minims of Adrenalin but the ring did not relax. Nevertheless, forceps were applied and moderate traction failed to bring the head down. The patient was returned to bed and given sedation, fluids, and antibiotics. Four hours later, the fetal heart tones became faint, and within the hour they disappeared. Thirty hours after the failed forceps, during which time her pains stopped and started again, the constriction ring was still present. Axis traction forceps were tried but failed. Three ampules of Spasmalgin, 1 ampule every ½ hour, failed to relax the ring. Twenty-four hours later, the ring was still present. Under deep ether anesthesia, axis traction forceps were again tried but they failed to budge the head. This was followed by a cesarean hysterectomy after a total labor of 70 hours.

The ring was found at the junction of the upper and lower uterine segments. It was necessary to incise the ring in order to deliver a stillborn male infant weighing 8

*Courtesy Dr. M. Wacker.

pounds, 9 ounces. The postoperative course was morbid with a temperature of 101° F. for 3 days. The patient was discharged on the ninth postoperative day in good condition.

Results

Table II demonstrates that of the 44 cases studied, 18 patients were multiparas and 26 were primiparas. Thirty-three had cesarean sections, and 11 were delivered vaginally. There was no maternal mortality, and 5 infants were lost. Two patients entered the hospital with fetal heart tones absent on admission.

TABLE II. ANALYSIS OF CASES

Total cases	44
Multiparas	18
Primiparas	26
Cesarean section	33
Vaginal deliveries	11
Maternal deaths	0
Fetal deaths	5*
Gross fetal mortality	11.3%
Corrected fetal mortality	6.8%

*Fetal deaths:

1. No fetal heart tones on admission. Section after 53 hours. Cervix dilated only 4 cm.
2. No fetal heart tones on admission. Breech presentation, amyl nitrite, delivery spontaneous.
3. Failed forceps, failed craniotomy. Spontaneous delivery 14 hours later.
4. Fetal heart tones disappeared after 43 hours, 30 minutes, of labor.
5. Fetal heart tones disappeared 6 hours after failed forceps, 4 hour second stage.

Table III demonstrates that a constriction ring was diagnosed in the first stage in 33 cases, and in the second stage in 11 cases; by external palpation in 14 cases, by intrauterine examination in 12 cases, and at cesarean section in 18 cases. In 40 cases the ring was in the region of the fetal neck, and in 3 cases the ring was below the presenting part. The presentation was either transverse or breech in the latter 3 cases. In only one case was the ring around an extremity.

TABLE III. DIAGNOSIS AND LOCATION

Diagnosis of Ring.—	
In the first stage	33
In the second stage	11
By external palpation	14
By intrauterine examination	12
At cesarean section	18
Location of Ring.—	
Around fetal neck	40
Below the presenting part	3
Around an extremity	1

TABLE IV. VAGINAL DELIVERIES

Spontaneous	3
Low forceps	3
Breech extraction	1
Spontaneous delivery of breech	1
Version and extraction	1
Failed forceps (one followed by cesarean hysterectomy)	2
Failed Dührssen's incisions	1
Duration of Labor	
Shortest	14 Hours
Longest	77 Hours

All cesarean sections were of the lower uterine segment type. Hysterectomy followed one cesarean section.

The data on vaginal deliveries are shown in Table IV. There were 4 spontaneous deliveries, one of them a breech. There were 3 low forceps deliveries, and 1 breech was given manual aid. There was 1 version and extraction. There were 2 failed forceps. Attempt at delivery following craniotomy failed, but eventual spontaneous delivery occurred. One case of failed forceps eventually was terminated by a cesarean hysterectomy and a dead baby (Case 2).

Deeper ether anesthesia was used in 2 cases, both in the second stage, with good results, one for a transverse presentation and the other for a low forceps delivery. Amyl nitrite was used in only 2 cases with good results in one. Amyl nitrite should be used more freely in the second stage of labor. Adrenalin was given in 8 cases without any effect upon the ring. Papaverine and Spasmalgin, which contains papaverine, were used in 6 cases, with good results in 4 instances. With the increased use of intravenous Pituitrin in prolonged labor, unsuspected constriction rings may become more pronounced. However, in this series, Pituitrin was used in only 3 cases. There was a suspected constriction ring in 1 case. This resulted in intensification of the ring.

Conclusions

1. A constriction ring is an infrequent but dangerous complication causing prolonged labor.

2. Its pathogenesis is not definitely known.

3. The diagnosis can be suspected if one finds any of the following cardinal signs:

In the first stage: (a) horizontal abdominal depression or groove, (b) loosely hanging cervix, especially during a uterine contraction, (c) the head easily rocked in the plevis.

In the second stage: (a) station recession of the presenting part during a contraction, (b) flaccid lower uterine segment and cervix.

4. The absolute diagnosis can easily be made by palpating the ring by intrauterine examination.

5. A traumatic delivery can be avoided if the ring can be relaxed before delivery.

6. Papaverine or Spasmalgin in the first stage and Amyl nitrite in the second stage may be of value in relaxing the constriction ring.

7. Forty-four cases are presented with no maternal mortality and a fetal mortality of 6.8 per cent.

8. The incidence of operative procedures was 84 per cent.

9. Treatment of constriction ring dystocia should be by cesarean section if antispasmodics have failed to relax the constriction ring during the first stage of labor.

10. If antispasmodics and deep ether anesthesia fail to relax the constriction ring during the second stage of labor, cesarean section is a lifesaving procedure.

I wish to thank Drs. Charlotte Kerr and Dale Collins, of the resident staff at Cook County Hospital, for photographing the constriction ring at the time of cesarean section, Case 1.

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Discussion

DR. JANET E. TOWNE.—Since this condition is fortunately encountered with relative rarity, the long-range extensive study presents a unique series of cases. To prevent deaths from constriction ring dystocia, there is a need for an awareness that such a condition exists. Dr. Fields has reviewed the formulated signs and symptoms that makes possible such a diagnosis. To those already mentioned, I should like to add another speculative sign which we have noted in our series of cases. Most authorities agree that intrauterine rings are an example of incoordinated muscular behavior in which the sympathetic and autonomic nervous systems act antagonistically. We have noted that this behavior apparently is not limited entirely to the uterus but also extends to involve the urinary bladder. It has been our clinical observation that: (1) Urinary retention appears early in these cases. (2) in spite of marked suprapubic abdominal distortion, the amount of urinary output decreased with periodic catheterization. (3) An intrauterine ring was often overlooked as the suprapubic distortion was attributed to a urinary retention.

By inserting retention catheters early in patients unable to perform voluntary micturition, we have been able to differentiate earlier the distended relaxed segment below the level of the intrauterine constriction ring.

The paper further illustrates an excellent example of what may be accomplished through statistical studies; the value is evidenced by the first table in which a marked decrease in the fetal and maternal mortalities are shown in the past five-year survey. Undoubtedly, chemotherapy has aided the reduction of the mortality rates but, apparently, greater strides have been accomplished by cesarean section since the operative incidence has risen from 0 to 75 per cent.

This fact seems to emphasize the wisdom of the decision that cesarean section be utilized as the treatment of choice for constriction ring dystocias. Why, then, is it necessary to wait several hours or days until the physical resources of the patient have been expended and the operative risk increased?

Unfortunately, it is not easy to advocate operative intervention, as this is in direct opposition to the obstetrical teaching in which "intelligent expectancy" is viewed with a reverence. However, I am not advocating cesarean section as an easy solution to all obstetrical problems, but merely suggesting that the indications for the operation be extended to include intrauterine rings.

DR. D. N. DANFORTH.—Unquestionably, many cases of constriction ring dystocia are not recognized as such, and it is for this reason that an occasional obstetrician claims that he never encounters this complication. There are two points upon which I should like to comment. First, I consider the use of amyl nitrite a very important recommendation. Most of us are accustomed to think of constriction rings in terms of epinephrine which of course is interdicted when cyclopropane anesthesia is being used. Since amyl nitrite appears to be at least as effective as epinephrine, and perhaps more so, and since it may be safely administered to a patient under any type of anesthesia, this should be an important addition to our obstetrical armamentarium.

The second point concerns the role of spinal anesthesia in the production of constriction rings. I am convinced that the low spinal anesthesia which is commonly employed for vaginal delivery enhances the uterine tone to a very considerable degree. I am also satisfied that after either an explosive labor or a prolonged one, the tendency to the development of constriction ring exists. Under these circumstances I believe that spinal anesthesia is contraindicated. I believe further that it is contraindicated in the presence of twins, breech presentation, and occiput posterior, since in all of these cases the development of a constriction ring during delivery may very seriously jeopardize the baby. I mention this with much feeling, since I have been caught, as it were, in all of these situations. A constriction ring in front of a second twin, with cord prolapsed through the ring, or a constriction ring about the neck before the aftercoming head may result in irreparable damage to the baby.

DR. FIELDS (Closing).—I was fortunate that early in my residency I was made aware of the fact that a constriction ring can be a dangerous complication in labor. For many years I was associated with the late Dr. Louis Rudolph and, as a result, I became constriction ring conscious. After twenty years, I must admit that I know very little about its origin.

I have tried to demonstrate that a constriction ring can be a cause for a prolonged labor, and that a diagnosis can be made. Any attempt at delivery from below, before the ring is relaxed with either anesthesia or drugs, may be dangerous for the mother and the infant.

I do not know enough about spinal anesthesia to discuss its effect on the formation of a constriction ring. Surely, with the increased use of spinal anesthesia in cesarean section and in vaginal delivery, we should see more rings, if spinal anesthesia is etiological. I do not believe that there is an increased incidence.

Amyl nitrite is an important drug which I had not appreciated until recently. Its effect in the second and third stages of labor is often dramatic.

I agree with White that the ring is present before labor has begun, and may be the first sign of incoordinate uterine action.

THE USE OF A CATION-ANION EXCHANGE RESIN IN THE CONTROL OF EDEMA AND EXCESSIVE WEIGHT GAIN IN PRENATAL PATIENTS*†

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THE history, rationale, chemistry, and mode of action of the ion exchange resins in the management of edema in various pathological states, including congestive heart failure, cirrhosis of the liver, and hypertension, have been previously reported.[1, 13] Scanty information exists, however, on the use of ion exchange resin in the control of edema and resultant excessive weight gain so commonly seen during the last trimester in the prenatal patient.[14, 15, 16]

There are many and various theories advanced as to the mechanism of edema formation, the greatest role being commonly attributed to increased electrolyte retention (principally the sodium ion) with associated retention of water. It is thought that this phenomenon is either due to an apparent increased reabsorption of sodium in the renal tubules,[15] or due only to a decreased glomerular filtration rate,[17, 18] in either case creating a positive sodium balance and resultant storage of the retained sodium ion with its bound water in the extravascular compartment. Other theories of edema formation include a deficiency of the total circulating serum protein[19, 20]; various hormonal agents, principally from the adrenal or pituitary glands[21, 22]; and a hypothetical agent as advanced by Weiss,[23] to mention a few. It is well recognized that prenatal patients, especially during the last trimester of pregnancy, are prone to develop edema, although in every other aspect the pregnancy seems to be progressing without incident. The edema, which is an especially common finding in the toxemias, may be present to a considerable degree, and yet may not be clinically demonstrable.[21] An excellent and complete review of the etiological factors of edema production in prenatal patients may be found in Dieckmann.[24]

It has been known since ancient times that elimination or restriction of sodium (salt) from the diet as a sole therapeutic measure usually produces improvement in the edematous or overweight patient. The sodium ion and its concentrations, as found in the intra- and extracellular compartments, have

*This work is not to be construed as necessarily reflecting the views of the Department of the Navy.

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been the subject of recent, intensive studies,[25] as have the effects of reduced-sodium diets in various pathological states.[26, 27, 28]

However, those involved in the management of prenatal patients realize the difficulties in convincing asymptomatic, healthy young women that it is necessary for them to restrict their sodium intake, thus placing them on the rather unappetizing, unpalatable "low-salt" or "salt-poor" diets. The results are generally discouraging.

The purpose of this paper is to attempt to evaluate critically the efficacy of a cation-anion exchange resin in the control of edema and excessive weight gain in prenatal patients, who, while on the resins, were allowed a more liberal salt intake (*circa* 5 Gm.) and approximately 1,500 to 1,800 calories daily, as opposed to the standard methods utilized in this clinic for weight gain control, which included a 1,030 calorie diet with salt restriction to 3.0 Gm. or less. In our experience adherence to the 1,030 calorie diet with rigid salt restriction has proved to be generally unsatisfactory during pregnancy, except for brief periods of time.

Previously reported studies[1-13] involving the use of cation exchange resins provide a new rationale in the control and treatment of sodium retention with its resultant edema and excessive weight gain. The resins interfere with the absorption of cations (sodium, potassium, magnesium, and calcium) or anions as the case may be from the gastrointestinal tract. In addition, it is evident that these products may block the reabsorption of considerable amounts of extravascular cations known to be secreted into the gastrointestinal tract. Once these cations enter into combination with the exchange resins they become transiently inabsorbable and are removed from the body via the stool. As this process is a nonselective one, other cations than sodium are removed from the body, which may result in an accompanying undesired negative balance of other cations in association with the desired negative sodium balance. Hypokalemia is the most frequent of such complications encountered. However, this problem may be anticipated or corrected by potassium replacement therapy in conjunction with the resin administration. Also to be considered in exchange resin therapy is the possibility of excessive salt depletion developing with its attendant acidosis. An excellent review of the dangers in exchange resin therapy may be found in the article by Dock and Frank.[1]

Method

The exchange resin used in this study was Carbo-Resin* (a product containing 12 per cent anion exchange resins; 29 per cent potassium salt of the carboxylic acid resin; and 59 per cent carboxylic acid resin). Potassium replacement therapy, when necessary, was accomplished by the use of Potassium Triplex* which is an oral potassium preparation supplying 15 meq. potassium per teaspoon of a highly absorbable mixture of potassium citrate, bicarbonate, and acetate.

In order to establish the fact that the weight gain for this clinic was within normal limits, the weekly weight gains of 500 prenatal patients from

*The Carbo-Resin, Potassium Triplex, and Cologel used in this study were made available gratuitously by Eli Lilly & Company, Indianapolis, Ind.

this clinic was tabulated and superimposed on the curves as given by Stander and Pastore[29] in their analysis of 2,935 prenatal patients (Fig. 1). The superimposed curve represents a cross section of this clinic and was not broken down into the three different normal (prenatal) classifications as was done by Stander and Pastore. As may be seen in comparison, the curve from this clinic closely approximates, but at a lower level, the lowest of the mass survey curves. Although the curve from this activity is by no means a statistical survey, it may be concluded that our weight control program compares very favorably with that of other clinics.

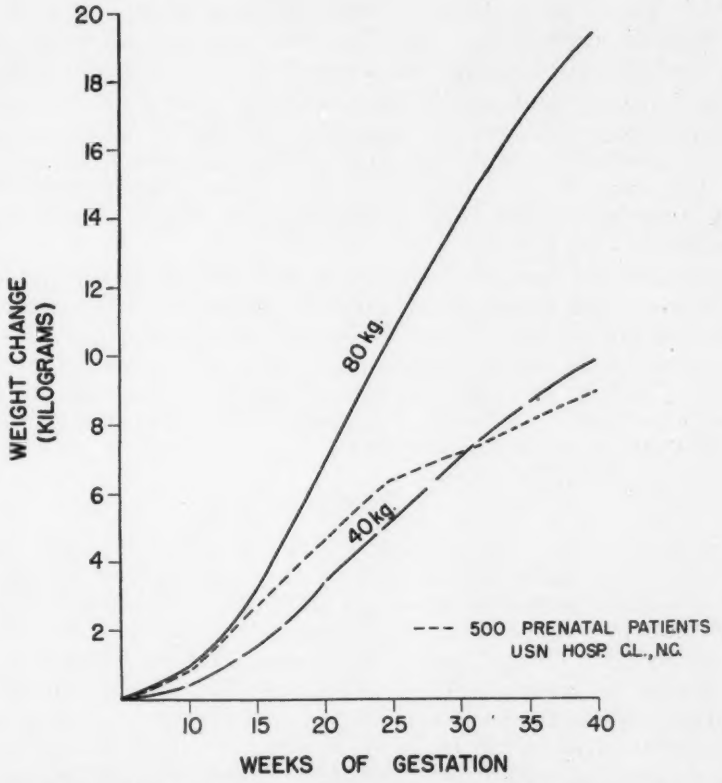

Fig. 1.—Weight gain curve of 500 patients from Prenatal Clinic, United States Naval Hospital, Camp Lejeune, N. C., compared with weight gain curves as given by Stander and Pastore.[29] The figures 80 kg. and 40 kg. are preconceptional weights.

Sixteen patients from the Prenatal Clinic, United States Naval Hospital, Camp Lejeune, N. C., exhibiting peripheral edema and/or excessive weight gain with no history of renal malfunction were hospitalized for study and clinical trial of Carbo-Resin. A one- to three-day period for control studies and diet regulation was followed by a five- to seven-day period of resin administration. Control studies were continued for one to three days after the resin was discontinued, following which the patients were discharged from the hospital to the prenatal clinic for follow-up, and, in some cases, further administration of the resin.

All weights included in this study were taken on the same "arm balance" type of scale which was standardized twice daily. Laboratory studies obtained throughout included: diet and food analysis according to Peters and Van Slyke[30]; urinary and blood chlorides, and carbon dioxide content of

serum, Scribner[31] (both repeatedly checked by the method of Van Slyke, Stadie, and Neill[30]); ammonia in urine, Van Slyke and Cullen[30]; and serum total protein with albumin/globulin ratio, quantitative urinary albumin, hematocrit, hemoglobin, and red cell counts after methods as described in Gradwohl.[32] A Beckman DU spectrophotometer with flame attachment (Model 9200) was used for the determination of sodium and potassium in food, body fluids, and feces.

A visual dye (carmine red) was used as a fecal marker at beginning and end of resin administration. All blood, urine, and feces were collected in Pyrex glass containers which had been previously coated with a silicone (Desicote*). These were washed with distilled water between samplings. Repeated analysis showed that the Desicoted containers did not "retain" or "keep" any sodium or potassium contamination from previous samples.

The "salt-free," "salt-poor," and "regular" diets offered at the U. S. Naval Hospital were analyzed and found to contain 1.0, 2.0, and about 6.0 Gm. of sodium, respectively. Although individual meals varied as much as 25 per cent, repeated analysis on a long-term basis showed little variation. All patients were ambulatory and their diets were one of the above standard diets of the hospital.

The Carbo-Resin was administered in the vehicle of the patient's choice, including water, milk, fruit juice, various carbonated beverages, or in some cases it was mixed with the food. Electrocardiograms, including standard, limb, and chest leads, were taken on all patients before and at various intervals during and after resin therapy. Clinical evaluations of the patients were done twice daily. All edema estimation and evaluation were done by one of us (J. P. B.) to ensure uniformity.

Results

Sixteen hospitalized patients were studied and given the resin. Fig. 2 represents the data gathered on one of the hospitalized patients (M. R.). Following a control period of two days the patient was started on 48 Gm. of the resin daily which she tolerated without difficulty. The control laboratory work was essentially normal and it was noted that on admission the patient exhibited 4 plus peripheral edema. Blood studies on the fourth day of the administration of the Carbo-Resin showed essentially no change except that the serum sodium had fallen from 141.8 meq. per liter to 135 meq. per liter while the serum potassium had remained essentially unchanged. As the patient began to lose weight the blood pressure fell, in this case the systolic more than the diastolic, while the urinary output increased. This probably reflects the renal efforts to excrete anions which were in excess following the removal of base (sodium, potassium, etc.) from the body via the stool. As may be seen in the urinary and fecal sodium and potassium curves, the urinary concentrations of both these cations fell as the fecal concentration rose. In this case, the urinary sodium values fell to practically nothing with a corresponding rise in the fecal sodium. Probably the initial rise in urinary potassium concentration was due to the increased potassium ingestion, as it is to be remembered that Carbo-Resin is fortified with potassium (having negligible sodium content). This fact would also cause a rise in the fecal potassium.

These data illustrate that Carbo-Resin markedly depletes the body stores of sodium, and, to a much more significant degree, also depletes the potassium stores. The rapid loss of large amounts of potassium from the

*Trade-mark registered by Beckman Instruments, Inc.

body stores, as previously demonstrated by Martz and co-workers[2] employing an unbuffered resin, was markedly reduced with the use of potassium-fortified Carbo-Resin. It would seem from our data that the potassium depletion does not become significant until (on the average) the patient had been on Carbo-Resin therapy four to five days. This fact is further emphasized by the marked rise in the fecal potassium excretion occurring on the third day of resin therapy. Further urinary and fecal samples collected on the fourth and sixth days post Carbo-Resin therapy (eleventh and thirteenth days, Fig. 2) show that the sodium and potassium levels were approaching preresin values. It would seem that the resin remains active in the bowel for a short time after cessation of therapy in prenatal patients, even though in this case the visual dye was noted in the stool 24 hours after resin was stopped. At the conclusion of the fifth day of resin administration, the peripheral edema was no longer manifest, and the routine laboratory determinations and electrocardiograms remained unchanged. From the day of admission to the day of discharge this patient lost 7.5 pounds. On discharge she stated that she felt much better,

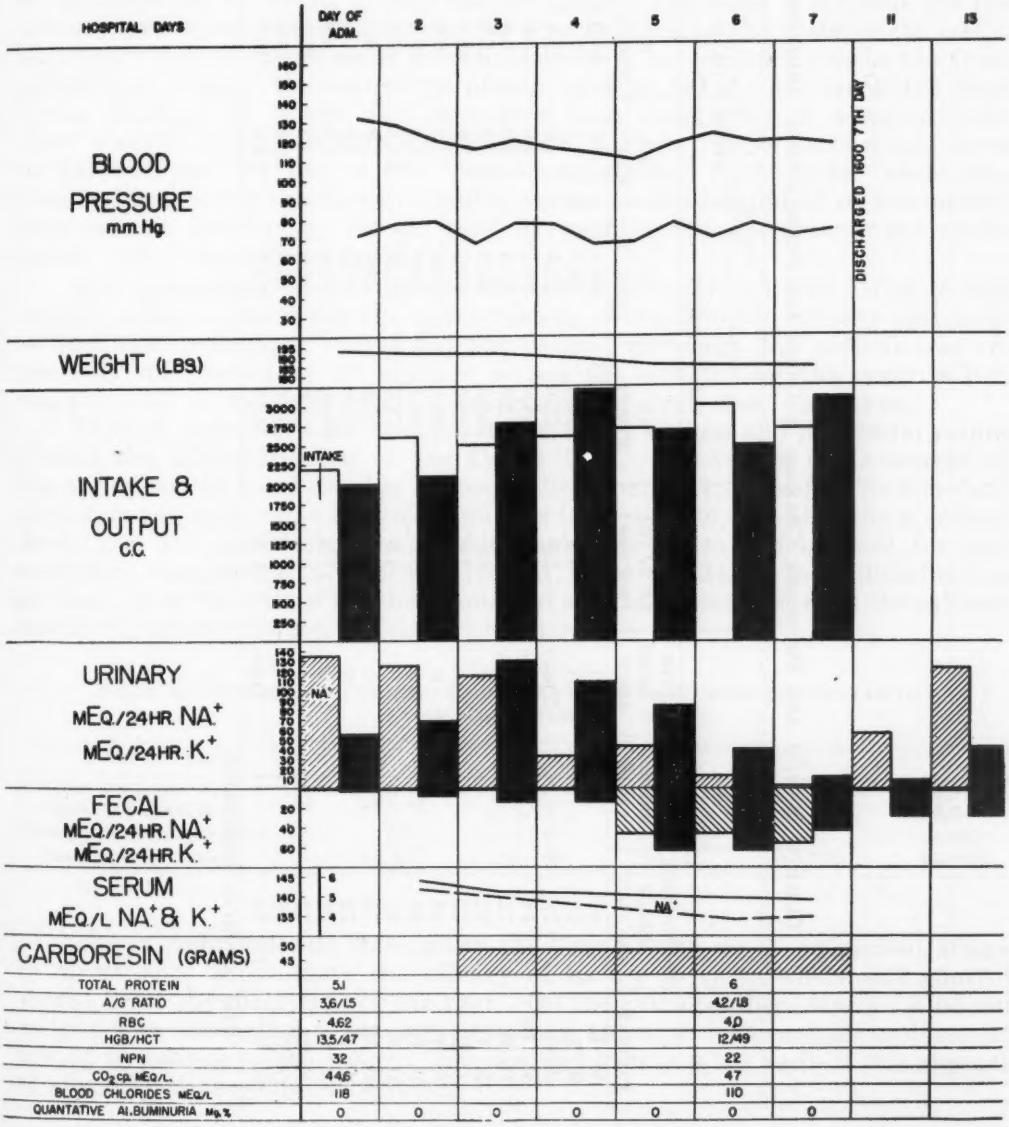

Fig. 2 (Case M. R.).—Shows changes in electrolytes, weight, and blood pressure due to ingestion of resin.

TABLE I. SODIUM AND POTASSIUM CHANGES IN URINE AND FECES DURING ADMINISTRATION OF CARBO-RESIN

PATIENT	CARBO-RESIN DOSAGE GM./DAY	EDEMA		WEIGHT CHANGE (5 DAYS) (POUNDS)	URINE				FECES			
					BEFORE RESIN		AFTER 5 DAYS' RESIN		BEFORE RESIN		AFTER 5 DAYS' RESIN	
		BEFORE RESIN	AFTER 5 DAYS' RESIN		NA. MEQ./L.	K. MEQ./L.	NA. MEQ./L.	K. MEQ./L.	NA. MEQ./ 24 HR.	K. MEQ./ 24 HR.	NA. MEQ./ 24 HR.	K. MEQ./ 24 HR.
M. R.	48	4+	0	-7.5	134.0	68.4	3.0	12.9	1.1	8.0	56.0	43.0
S. R.	72	3+	0	-9.5	35.6	38.0	1.2	11.4	2.4	8.0	30.0	23.0
S. O.	72	2+	Trace	-7.0	73.0	75.0	4.5	29.8	2.1	13.0	53.0	60.0
M. M.	48	4+	Trace	-6.0	56.0	96.0*	5.0	73.0	3.0	17.0	89.0	80.4
D. B.	72	3+	Trace	-3.0	72.0	57.0	4.5	6.0	2.3	13.7	92.8	91.0
M. O.	72	4+	0	-5.0	118.0	63.0	5.2	45.0	1.4	12.4	31.0	30.0
J. H.	72	3+	Trace	-3.0	115.0	43.0	15.0	33.0	3.4	15.3	10.0	44.7
R. T.	48	2+	0	-6.0	66.0	104.0*	3.2	8.6	2.2	21.0	66.0	100.0
P. B.	48	Trace	0	-8.0	63.8	44.6	5.4	22.2	4.1	12.3	47.0	43.4
H. S.	72	2+	0	-4.0	76.0	110.6*	11.8	43.0	4.1	17.5	9.7	87.3
B. M.	72	Trace	0	-6.0	53.0	30.0	2.9	4.0	2.3	5.1	62.0	11.7
A. D.	72	2+	0	-9.25	83.0	16.5	3.5	20.0	3.4	25.0	53.4	64.8
R. S.	72	4+	0	-11.0	200.0	37.0	3.5	8.0	11.5	9.4	15.0	15.3
E. M.	72	Trace	0	0	54.0	36.0	4.3	30.0	-- -	-- -	-- -	-- -
G. L.	72	1+	Trace	+1.25	50.0	33.5	52.4	34.8	1.7	11.0	7.9	27.4
S. V.	72	3+	Trace	-8.0	62.1	16.1	16.0	30.0	2.0	15.0	65.0	72.0

*Oral potassium supplement.

although on admission she emphatically insisted that she felt well and saw no reason for entering the hospital. At the beginning of the second day of Carbo-Resin administration she stated that the stiffness of her hands and feet was disappearing and on discharge they felt normal for the first time in two months. In conjunction with the resin administration she was placed on Metamucil* (1 teaspoon three times a day) and had no difficulty with bowel evacuation.

The pertinent data from the hospitalized series of patients are summarized in Table I. It was thought that a comparison of the control data to data obtained on the fifth day the patient had been on the Carbo-Resin would graphically illustrate the changes resulting from resin administration. Analysis of the data in every case showed that the clinically demonstrable peripheral edema was markedly reduced, and in all but one case there was significant loss of weight. Although there was a wide variation in the control urinary sodium values, after five days of Carbo-Resin therapy the values for all patients fell to within a very narrow range. The same is not true for the urinary potassium values. As may be seen in some of the cases, there was a significant fall in the urinary potassium, with a concomitant rise in the fecal potassium. Again, the values we obtain parallel but do not reach the high levels obtained by Martz and associates[2] who were using in some of their cases a carboxylic resin with no potassium content. These facts would seem to indicate that the use of the "potassium-fortified" Carbo-Resin, while producing the desired therapeutic results, decreases the likelihood of concurrent hypokalemia developing. At the onset of resin therapy, the urinary potassium output rose followed by a rapid fall.

It is interesting to note that in the one patient (G. L.) who failed to lose weight while on the resin, the characteristic changes in the urinary and fecal sodium and potassium values did not occur. Although the patient was repeatedly questioned as to whether or not she was taking the resin, which she affirmed, it was impossible to ascertain that each dose was taken.

Table II represents the changes in the serum sodium and potassium values during the administration of the Carbo-Resin. All values are averages of the values of the total number of hospitalized patients studied. The standard deviation for each value is listed, and it is important to note that the standard deviations are uniformly small. Although this series is too small for any statistical conclusions to be drawn from it, these results are most illuminating in that the serum values for these ions had small fluctuations while the urinary and fecal values changed through wide ranges.

TABLE II. SODIUM AND POTASSIUM CHANGES IN SERUM DURING ADMINISTRATION OF CARBO-RESIN*

DAYS ON RESIN	1	2	3	4	5
Sodium meq. per liter	137.5	137.5	136.94	135.5	135.44
Standard deviation	±3.7	±2.85	±2.71	±2.06	±3.6
Potassium meq. per liter	4.87	4.54	4.74	4.57	4.45
Standard deviation	±0.157	±0.168	±0.145	±0.172	±0.108

*N = 16.

Thirty-eight patients were given the Carbo-Resin on an outpatient status in an attempt to evaluate the efficacy of its use in cases where salt control would be at the discretion of the user. On the average, there was a 1.5 pound weight loss following a ten-day period of therapy. The usual problem of trying to convince each patient that she should ingest the resin in the absence of any subjective symptoms was met.

*G. D. Searle Company, Chicago, Ill.

TABLE III. DATA FROM OUTPATIENTS ON CARBO-RESIN THERAPY

PATIENT	TOTAL WT. GAIN	NO. GRAMS RESIN	DIET	NO. DAYS ON RESIN	WT. LOSS (POUNDS)	EDEMA
E. A.	13.5	72	CRD*	3	- 1.5	2+ - 2+
C. B.	6.75	72	CRD	4	- 3.5	1+ - 0
		60	CRD	6	+ 1.25	3+ - 1+
F. B.	30.0	72	CRD	2	+ 1.25	0 - 0
M. B.	16.0	72	CRD	3	- 3.75	1+ - 0
D. C.	43.25	64	CRD	3	- 3.75	2+ - trace
		64	CRD	3	- 1.50	Trace - 0
C. D.	16.0	56	CRD	7	- 1.50	3+ - 1+
		56	CRD	7	+ 2.25	1+ - 2+
		56	CRD	6	- 2.25	2+ - trace
J. D.	7.5	72	CRD	6	- 7.0	3+ - 0
E. E.	29.0	96	CRD	7	0.0	1+ - 0
		72	CRD	4	0.0	0 - 0
		48	CRD	3	- 0.5	0 - 0
		56	CRD	7	- 3.0	2+ - 0
		56	CRD	9	+ 4.0	0 - 0
		56	CRD	5	- 1.0	0 - 1+
B. E.	13.0	50	1,030	7	+ 1.25	0 - 0
V. F.	31.0	72	CRD	7	+ 1.25	1+ - trace
		72	1,030	4	+ 0.50	Trace - trace
		63	CRD	6	+ 1.50	Trace - 0
		72	CRD	7	- 2.0	1+ - 0
		48	CRD	7	- 2.0	Trace - 1+
B. G.	23.0	48	CRD	7	+ 2.0	0 - 0
		72	CRD	7	- 3.0	0 - 0
		72	1,030	7	+ 2.0	0 - 0
B. H.	22.5	72	CRD	7	- 4.0	1+ - 0
		72	CRD	4	- 1.5	0 - trace
		96	CRD	7	- 5.0	2+ - trace
		73	CRD	7	- 0.5	Trace - trace
		48	CRD	7	- 0.5	Trace - trace
		48	CRD	7	- 0.5	Trace - 1+
		48	CRD	7	+ 0.75	Trace - 1+
		72	CRD	8	+ 2.75	1+ - 2+
		96	CRD	7	+ 3.5	2+ - 1+
D. K.	11.5	72	CRD	7	- 8.0	1+ - 0
J. J.	30.0	72	CRD	7	- 5.0	1+ - 0
		48	CRD	7	- 1.0	0 - 0
		48	CRD	4	+ 2.0	0 - 0
M. E. K.	35.25	96	CRD	2	- 1.0	2+ - 1+
		72	CRD	7	- 3.0	3+ - 0
M. K.	15.25	72	1,030	5	- 2.75	2+ - trace
A. L.	19.0	72	CRD	3	- 3.50	2+ - trace
		72	CRD	7	- 6.50	1+ - 0
		48	CRD	4	+ 2.50	0 - 2+
		48	CRD	7	- 0.50	2+ - 2+
		63	CRD	4	+ 4.0	2+ - 2+
		72	CRD	7	+ 1.0	2+ - 1+
		72	CRD	7	- 3.0	1+ - 0
		72	CRD	3	+ 3.50	0 - trace
G. M.	22.5	48	1,030	7	- 1.25	0 - 0
		48	1,030	6	- 3.0	0 - 0
J. D.	24.5	72	CRD	7	- 1.0	2+ - 2+
		72	Liquid D	4	- 2.0	2+ - 1+
P. R.	38.0	48	CRD	7	- 2.0	0 - 0
		48	CRD	3	+ 3.0	0 - 0
		72	CRD	7	+ 3.0	0 - 0
M. R.	25.25	72	CRD	7	- 4.0	Trace - 0
		72	CRD	7	- 6.0	2+ - 1+
		48	CRD	9	+ 3.0	1+ - trace
M. S.	16.25	72	CRD	7	- 1.25	2+ - 1+
		48	CRD	7	- 0.50	1+ - 1+

*Carbo-Resin diet calculated to 5 Gm. salt and 1,500-1,800 calories.
†Hospitalized patients subsequently treated as outpatients.

TABLE III—CONT'D

PATIENT	TOTAL WT. GAIN	NO. GRAMS RESIN	DIET	NO. DAYS ON RESIN	WT. LOSS (POUNDS)	EDEMA
M. S.	14.0	48	Unlimited	9	+ 2.75	0 - 1+
		96	CRD	7	- 4.25	1+ - 0
		96	CRD	7	- 2.0	0 - 0
		96	Liquid D	5	- 8.50	2+ - trace
		48	CRD	7	- 0.50	Trace - 0
		48	CRD	7	+ 4.5	0 - 0
		72	CRD	7	- 1.0	0 - trace
P. V.	33.0	72	CRD	2	- 3.25	2+ - 0
		40	CRD	7	0.0	0 - 0
J. W.	7.50	48	CRD	7	- 1.0	1+ - trace
		56	CRD	2	+ 1.0	Trace - 1+
		56	CRD	7	0.0	1+ - trace
B. T.	28.0	56	CRD	7	- 2.50	3+ - 1+
		56	CRD	10	+10.0	1+ - 1+
		80	CRD	7	+ 1.5	1+ - 1+
		80	CRD	5	- 8.0	1+ - 0
M. C.	23.0	64	CRD	6	- 5.0	0 - 0
		64	CRD	7	- 2.0	0 - 0
B. C.	30.0	56	CRD	7	- 5.0	0 - 0
		56	CRD	7	- 4.25	1+ - 0
M. T.	25.0	80	CRD	7	- 2.25	2+ - trace
		48	CRD	5	0.0	Trace - 0
		48	CRD	7	- 3.50	0 - 0
†S. V.	19.0	96	CRD	6	- 0.75	3+ - 3+
		96	CRD/Liquid D	12	-15.0	3+ - 0
†M. F. R.	31.75	96	CRD	7	- 0.5	1+ - 1+
		72	Liquid D	7	+ 0.75	1+ - 1+
		72	CRD	9	+ 1.0	1+ - 2+
		96	CRD	10	0.0	2+ - trace
†E. M.	37.50	72	CRD	8	- 1.5	Trace - 0
		72	CRD	8	+ 3.5	0 - 0
		72	CRD	3	- 3.0	0 - 0
		72	CRD	7	+ 1.5	0 - 0
		72	CRD	10	+ 0.5	0 - 0
†M. G.	26.5	48	CRD	7	- 4.50	Trace - 0
		48	CRD	7	- 1.0	0 - 0
		72	CRD	5	+ 2.0	0 - 0
†S. O.	18.5	72	CRD	7	- 2.50	2+ - 0
†D. B.	36.25	8	CRD	7	+ 1.0	3+ - 3+
		96	CRD	3	+ 2.50	0 - 1+
†R. T.	37.50	48	CRD	7	+ 1.75	Trace - 1+
		96	CRD	11	+ 1.25	1+ - 0
†J. A.	32.50	72	CRD	7	+ 1.0	1+ - 1+
		72	CRD	7	0.0	1+ - trace
		72	CRD	7	+ 3.0	Trace - trace
		72	CRD	7	0.0	Trace - trace
†A. D.	47.0	72	CRD	6	- 1.5	Trace - 0
		72	CRD	2	- 1.75	1+ - 0

The clinical course of these patients was followed by interval blood studies and electrocardiograms in anticipation of the possibility of the development of electrolyte imbalance, particularly hypokalemia. Daily dosage range varied from 48 to 96 Gm. of Carbo-Resin. Sixteen per cent of this series were given supplemental oral potassium prophylactically. In no case was there any laboratory or clinical evidence of hypokalemia.

The results from this series are summarized in Table III, the most significant finding being the uniform loss of edema. In some cases, improvement of the edema was quite remarkable in both degree and rapidity. However, in several instances, despite complete disappearance of the edema, the patient continued to gain weight.

Comment

Although the mechanism or mechanisms of edema production are at best poorly understood, generally speaking the principles of therapy are the same regardless of cause and have not altered materially in recent years. Until the advent of the ion exchange resins as a therapeutic measure, the low-sodium diet, with the dangers attendant upon altering the electrolyte-water equilibrium of the body, was the most common form of therapy. As adjuncts, high-protein diets, oral ammonium chloride, parenteral mercurial preparations, xanthine derivatives, and various drugs having a primary action on the cardiac musculature (digitalis) were used. Recently, as pointed out in several articles,[27, 28, 33] the "low-salt" syndrome and the abuses of the low-sodium diet have been emphasized. As a result the pendulum has begun to swing away from the regime of rigid salt restriction.

When the ion exchange resins are utilized for therapy, the dietary restrictions may be relaxed somewhat, and indeed the resins are more efficient when the dietary sodium is increased. Economically and gastronomically the burden placed upon the patient becomes less severe, allowing her to live a more normal life.

The general effect of the resins on the blood pressure was to lower it significantly. This response in some cases was pronounced in our series of prenatal patients after the usual methods of therapy had been tried with unsatisfactory results. The ion exchange resins in the human being are directly as efficient as the rate at which they move through the intestinal tract. This fact became apparent, particularly in the outpatient group, where several patients started on the resin showed a slight decrease in the peripheral edema with no significant weight loss in the absence of bowel movements. However, with the establishment of satisfactory bowel function, the decrease in peripheral edema and loss of weight became much more pronounced. The control of the bowels became a severe problem as the dosage of the resin increased. Generally, one of the hydrogels (Metamucil, Cologel, etc.) sufficed to restore bowel function to near normal. In only two cases was it necessary to hospitalize patients for treatment of obstipation. Two patients reported that the Carbo-Resin incited diarrhea. On the whole the Carbo-Resin was tolerated well in therapeutic doses, although in several instances nausea and gagging associated with its administration necessitated temporarily decreased doses or cessation of therapy.

Serial electrocardiograms taken on all patients showed that in only four instances were there changes suggestive of hypokalemia. Oral potassium was given with rapid response, as reflected in the return of the electrocardiograms to normal. In no patient who was given prophylactic oral potassium therapy was there any electrocardiographic evidence of potassium imbalance, even in the presence of relatively large doses of Carbo-Resin. One case (S. R.) in which electrocardiographic changes compatible with hypokalemia developed prior to the institution of potassium therapy is to be published as a case report.

The question of optimum therapeutic dosage of Carbo-Resin was not adequately determined in this study. However, there were several impressions obtained. Generally the inpatients required less of the resin than the outpatients. In the inpatient series it is to be noted that some patients responded as well on 48 Gm. of resin daily as did others receiving 72 Gm. However, several patients started on therapy at the 48 Gm. level showed no response until the dosage had been progressively increased to 72 Gm., following which they promptly exhibited a good clinical response. In the outpatient series the response to various dosage levels fluctuated widely, not only from patient to patient, but also in individual patients, from week to week during the prenatal course. This fact is at least partially accounted for by the uncertainty of the amount of the prescribed resin dosage ingested by the patient as well as by the wide variations of the dietary sodium intake.

Electrocardiograms, x-rays, calcium-phosphorus ratios, and serum potassium and sodium studies, in addition to the usual laboratory determinations, taken on four babies delivered from patients who had been on relatively large doses of the resin during the period immediately prior to delivery showed no evidence of electrolyte imbalance. The babies all progressed well and clinically the pediatrician found no evidence of any electrolyte disturbance.

Conclusions

1. Carbo-Resin (a mixture of 12 per cent anion, 29 per cent potassium, and 59 per cent hydrogen resin) has been administered to 16 hospitalized and 32 outpatient prenatal patients exhibiting edema and/or excessive weight gain during the last trimester of pregnancy.

2. Utilizing the anion-cation exchange resin (Carbo-Resin), it was possible to reduce or eliminate the edema so commonly found in the prenatal patient, after established methods, short of hospitalization on liquid diets and bed rest and treatment with diuretics, had produced little or no result. Our findings indicate that the Carbo-Resin is more effective in the reduction of peripheral edema (with a relatively increased salt ingestion) than in the control of excessive weight gain in the prenatal patient. In the former instance, the clinical results were uniformly excellent, although weight loss did not always accompany reduction of edema.

3. Two inherent dangers to be anticipated in the use of any exchange resin are the development of hypokalemia and the "low-salt" syndrome with its attendant acidosis. Prolonged administration of the exchange resins requires a diet adequate in potassium content, with serial electrocardiography and repeated blood chemistry determinations. However, for short-term dosage (not exceeding five days in our series) it may be given safely. For longer periods of therapy it is felt that supplemental oral potassium therapy should be administered in conjunction with the exchange resins. Electrocardiography was considered most important in monitoring any severe fluctuations in potassium levels.

4. The exchange resins should not be used in patients with severe renal tubular impairment unless they can be followed with adequate laboratory work in the hospital.

5. The efficacy of the exchange resins was found to be directly proportional to the frequency of bowel movements. Care should be taken to ensure adequate bowel exacuation while the exchange resins are being administered.

We wish to express our sincere appreciation to Dr. Howard T. Karsner, Medical Research Advisor to the Bureau of Medicine and Surgery, and to Captain C. B. Galloway, Medical Corps, United States Navy, and the Staff of the Naval Medical Field Research Laboratory, Camp Lejeune, N. C., for the aid and advice rendered during the preparation of this paper; to Lieutenant Norman Makous, Medical Corps, United States Naval Reserve, Staff, United States Naval Hospital, Camp Lejeune, N. C., for interpreting the electrocardiograms; and to Lieutenant Commander A. T. Henderson, Medical Corps, United States Navy, Chief of Pediatrics, United States Naval Hospital, Camp Lejeune, N. C., for evaluating the newborn infants.

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OBSERVATIONS ON THE RENAL TUBULAR REABSORPTION OF URIC ACID

I. Normal Pregnancy and Abnormal Pregnancy With and Without Pre-eclampsia

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THE specific toxemia of pregnancy, pre-eclampsia, is not characterized by any specific biochemical changes in the blood. Certain patients may exhibit hemoconcentration, hypoproteinemia, reduced carbon dioxide combining power, or hyperuricemia. None of these is invariably found. When present, they are usually manifestations of severe pre-eclampsia. The factors responsible for these changes are unknown, despite much investigative effort. Certainly none of these changes are etiological, but it is hoped that the identification of the mechanisms responsible for these conditions of the blood might provide some information concerning the etiology or pathogenesis of acute toxemia.

The hyperuricemia of acute toxemia has attracted considerable study. Inasmuch as hyperuricemia can result from increased production or decreased excretion of uric acid, both phases of urate metabolism have been investigated. Unfortunately, studies of urate production have been based on the determination of the 24 hour urinary urate excretion of pregnant patients on a low purine diet. This investigative approach is unsatisfactory for two reasons. Increased urinary urate may arise from either increased catabolism of nucleoprotein (e.g., leukemia) or from an abnormal rate of synthesis (e.g., gout).[1] Furthermore, the 24 hour urinary urate content is determined by kidney function as well as by the metabolic rate. We conclude, therefore, that no information is available concerning the metabolic production of uric acid in pregnancy toxemia.

The renal excretion of urate is abnormal in pre-eclampsia. The data of Schaffer, Dill, and Cadden[2] implied that this might be true. Chesley and Williams,[3] in 1945 were the first to apply specific and discriminating techniques to this problem. In a study of 10 normal, 8 severely pre-eclamptic, and 2 eclamptic pregnant women, they concluded that the hyperuricemia of their patients with acute toxemia was the result of diminished uric acid clearance. This decrease in the urinary excretion of urate was caused by reduced glomerular filtration and increased tubular reabsorption. Both factors were considered equally responsible.

Material

We were led to repeat this work on 27 nontoxemic patients and 14 pre-eclamptic women because of several observations. First, reduced glomerular filtration is manifest in only some toxemic pregnant women. It is not charac-

teristic of mild acute toxemia. Second, hyperuricemia is usually absent in mild cases of pre-eclampsia. It was our purpose, therefore, to determine the state of the renal excretion of urate in mildly pre-eclamptic patients in whom one might expect the glomerular filtration rate and the plasma concentration of urate to be within normal limits.

The clearance of mannitol was used as a measure of the glomerular filtration rate. Simultaneous renal clearances of uric acid (Cua) and mannitol (Cm) were obtained during the last trimester of pregnancy. Plasma and urinary uric acid determinations were performed by the method of Archibald.[4] Mannitol was measured by the method of Smith, Finkelstein, and Smith.[5] The procedures were initiated between 8:30 and 9:30 A.M. and completed before noon. Multiple, successive, short (15 to 20 minutes) urine collection periods were utilized, and the urine flow was maintained at greater than 4.00 c.c. per minute. With the exception of 3 control patients and 2 toxemic women, the subjects were fasting at the time of the study.

The control group of 27 antepartum patients consisted of 8 normal and 19 abnormal pregnant women as listed below. None of these women developed hypertension during pregnancy or in the puerperium.

Normal pregnancy	8
Excessive weight gain	5
Vaginal bleeding	4
Iron deficiency anemia	3
Diabetes, uncomplicated	2
Unexplained intrauterine fetal death	2
Premature rupture of membranes	1
False labor	1
Pulmonary tuberculosis	1

The 14 pre-eclamptic patients all demonstrated significant elevation of the blood pressure in the last trimester of pregnancy. In every case, the blood pressure had risen to over 140/90 in a significant number of observations. All of the patients were admitted to the hospital by members of the resident or attending staff in the course of their clinical care. None were hospitalized for the purpose of performing these tests. Twelve patients had minimal hypertension and were considered to have mild pre-eclampsia. Of this group, 4 had proteinuria, 9 had edema, and none had either severe or persistent headache or any visual or gastrointestinal symptoms. The remaining 2 patients, classified as having severe pre-eclampsia had rather marked elevation of the blood pressure, proteinuria, and edema, in addition to severe headache and visual complaints. One of these 2 patients had nausea and vomiting.

Results (Table I)

Plasma Uric Acid.—The plasma urate concentration was below 6.0 mg. per cent in every member of the control group. Eleven (79 per cent) of the 14 pre-eclamptic patients also had plasma urate levels below 6.0 mg. per cent. These results support the observation that hyperuricemia is *not* characteristic of mild pre-eclampsia.

Glomerular Filtration Rate.—There was some decrease in the average glomerular filtration rate of the pre-eclamptic group when compared to that of our normal antepartum patients. This reduction amounted to 18.7 per cent, and we must conclude that the glomerular filtration rate is well maintained in mild preeclamptic toxemia.

Uric Acid Clearance.—The uric acid clearances of the pre-eclamptic patients were reduced severely. The results obtained in this group demonstrated a decrease of 47.6 per cent when compared with the average clearance of the normal controls.

TABLE I. INDIVIDUAL RESULTS OF ALL PATIENTS IN STUDY

DIAGNOSIS	BODY SURFACE SQ.M.*	PLASMA URIC ACID MG. %	CUA C.C./MIN.†	CM C.C./MIN.†	$\frac{CUA}{CM} \times 100$
Mild pre-eclampsia	1.83	5.10	6.75	79.0	8.6
	2.06	4.58	14.32	187.2	7.6
	1.54	5.62	9.46	147.0	6.4
	1.96	4.30	8.65	116.3	7.6
	2.07	4.27	9.48	155.5	6.1
	1.79	5.44	11.98	128.4	9.3
	1.81	5.75	8.18	167.2	4.9
	1.73	8.65‡	4.83	97.0	5.0
	1.70	4.50	8.44	125.1	6.7
	1.48	5.14‡	5.68	119.8	4.7
	1.37	3.34	7.78	97.0	8.0
	1.84	3.90	7.80	115.9	6.7
Severe pre-eclampsia	1.48	6.83	10.49	111.9	9.4
	1.88	11.10‡	3.78	92.0	4.1
Normal pregnancy	1.53	3.24	17.10	157.3	10.9
	1.56	4.16	19.96	166.0	12.0
	1.83	2.93	18.23	170.4	10.7
	1.57	4.03	10.88	131.2	8.3
	1.70	3.08	12.71	137.4	9.2
	1.48	2.74	14.79	116.1	12.7
	1.26	5.36	19.48	157.2	11.1
	1.49	4.02	17.05	187.5	9.2
Excessive water retention	1.73	3.82	18.82	162.5	11.6
	1.68	5.35‡	13.40	87.4	15.3
	2.01	3.93	14.42	149.5	9.7
	1.65	5.38	19.85	145.5	13.6
	2.10	3.50	16.81	162.2	10.4
Vaginal bleeding	1.53	3.13	24.40	152.5	16.0
	1.48	4.13	13.96	122.1	11.4
	1.52	5.11	5.24	103.5	5.0
	1.71	4.60	25.71	139.9	18.4
Iron deficiency anemia	1.77	2.77	22.40	165.0	13.6
	1.70	5.50‡	9.25	94.5	9.8
	1.52	1.98	26.30	144.0	18.2
Uncomplicated diabetes	1.87	5.04	18.63	142.9	13.0
	1.53	2.80	20.75	127.1	16.3
Antenatal fetal death	1.58	5.72‡	14.80	115.0	12.9
	1.62	3.36	16.20	135.6	11.9
Ruptured membranes	1.56	3.55	13.00	130.6	9.5
False labor	1.67	3.37	15.40	153.8	10.2
Pulmonary tuberculosis	1.26	2.67	20.45	126.2	16.2

*Calculated from measured height and stated prepregnancy weight.
†Corrected to 1.73 sq. M. of body surface.
‡Received ribose nucleic acid prior to the procedure.

Tubular Reabsorption of Uric Acid.—The percentage excretion of filtered uric acid is decreased in acute toxemia. The pre-eclamptic patients excreted 6.8 ± 1.7 per cent of the filtered urate as compared with 10.5 ± 1.6 per cent in the normal pregnant women, and 12.8 ± 3.4 per cent in the abnormal, but nontoxemic patients.

In summary, the results demonstrated that patients with early mild pre-eclampsia manifest normal plasma urate concentrations and relatively normal glomerular filtration rates (Table II), but the clearance of uric acid is reduced because of the excessive renal tubular reabsorption of uric acid (Fig. 1).

Comment

The data of Chesley and Williams and our results both indicate that patients with pre-eclamptic toxemia and nontoxemic pregnant women represent differ-

ent statistical populations in respect to the tubular reabsorption of urate. The individual values overlap to such a degree that the procedure, performed as outlined, cannot serve as a specific diagnostic test. However, the significance of the results at this time lies not within the province of securing a diagnostic test, but rather in providing another starting point in the study of the mechanism of the excessive reabsorptive capacity of the renal tubules of patients with pre-eclamptic toxemia.

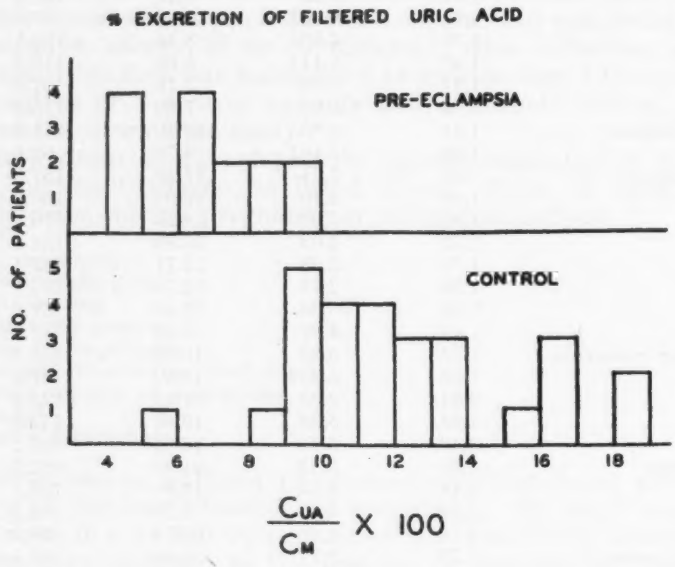

Fig. 1.

Why does the renal tubule reabsorb urate excessively in women with pregnancy toxemia? There is no certain answer. A variety of therapeutic substances are uricosuric, but known, naturally occurring uricosuric agents are few. In specific experimental circumstances, the diet and ACTH play a role in controlling the rate of tubular function in respect to urate excretion. ACTH increases the glomerular filtration rate and reduces the tubular reabsorption of urate resulting in increased urate excretion.[6] In pre-eclampsia, the uric acid clearance is reduced as a result of enhanced tubular reabsorption of urate with either normal or decreased glomerular filtration. Therefore, these results lend no support to any hypothesis concerning pre-eclampsia that assigns increased glucocorticoid activity, secondary to ACTH production, an etiological or pathogenetic role.

It has been demonstrated by Lennox[7] that fasting produces a marked decrease in the excretion of urate associated with hyperuricemia. He inferred, therefore, that fasting produces decreased renal excretion of urate. Inasmuch as other nitrogenous substances such as urea were not retained, the impaired excretion of urate must have been the result of increased tubular reabsorption. This effect of fasting occurs rapidly and is obvious as early as the second day of the fast.

The changes in the renal excretion of urate produced by fasting are similar to those observed in patients with acute toxemia. The possibility exists, therefore, that some dietary substance that is physiologically uricosuric may not be available to the renal tubules of patients with pregnancy toxemia as the result of either excessive utilization or inadequate intake. This concept is, of course, purely speculative.

TABLE II. SUMMARY OF RESULTS

DIAGNOSIS	NO. PATIENTS	URIC ACID CLEARANCE C.C./MIN. AVERAGE	MANNITOL CLEARANCE C.C./MIN. AVERAGE	$\frac{CUA}{CM} \times 100$ AVERAGE
Normal pregnancy	8	16.03 ± 3.01	152.9 ± 23.2	10.5 ± 1.6
Abnormal pregnancy (nontoxemic)	19	17.36 ± 5.50	134.7 ± 22.4	12.8 ± 3.4
Pre-eclampsia	14	8.40 ± 2.77	124.2 ± 30.6	6.8 ± 1.7

Summary

1. The average plasma urate concentration and the average glomerular filtration rate of patients with mild acute toxemia are within normal limits.

2. Uric acid clearance in these patients is reduced as the result of excessive tubular reabsorption of urate.

3. Regardless of the severity of the toxemia, patients with pre-eclampsia commonly manifest excessive tubular reabsorption of urate.

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THE PROBLEM OF POSTMATURITY*

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POSTMATURITY is a problem that causes considerable annoyance to the woman who has gone two or three weeks past her expected date of confinement. There is little if any clinical significance to this miscalculation, either on the part of the physician, or on the part of nature, but all obstetricians appreciate the anxiety on the part of the patient, when she is long past her due date and there are no signs of labor. Concern is soon manifested by the patient that varies from thoughts of the necessity of a cesarean delivery to the possible death of her baby in utero. These worries must be judged by the physician and proper counsel given the patient.

Material

A two-year study has been made to evaluate the problem of postmaturity. Labor was not induced in any patient, regardless of the postmaturity, except where there were symptoms of toxemia, diabetes, or definite medical indications for terminating the pregnancy. I was prepared to expect some extremely large babies, a number of long labors, and, as some articles in the literature warned, fetal deaths.

In a series of 736 consecutive private patients, with the history carefully taken personally, there were 71 cases in which the postmaturity went beyond 14 days. This represented approximately 10 per cent of the entire group. The material is tabulated in Table I and includes the age of the patient, parity, the number of days that she was overdue, the number of hours of labor, the type of delivery, and the weight and sex of the infants.

Most clinics consider 4,500 grams as the division for large babies. Using that criterion, only 5 infants in this series would qualify as large babies. However, this figure was reduced to include all infants 9 pounds or over. All but 2 of these large babies were delivered spontaneously; the 2 exceptions were outlet forceps deliveries.

The relationship between postmaturity and excessive size of the infant has been analyzed with special clarity by Calkins. He reported that the growth curve for both placentas and babies follows the general form of an elongated *S*. Increase in size continues throughout the pregnancy, but contrary to the impression given by the Hasse formula, this growth is not at a uniform rate. Growth being rapid up to the two hundred sixtieth day is much less rapid from the two hundred sixtieth to the two hundred eightieth day, and the increment after full term is very small. For the fetus this weight increase is only 130 grams for the last twenty days of postmaturity. Calkins then rightly emphasizes the following practical point: "The obvious disadvantages of inducing labor in the presence of an unprepared cervix cannot possibly be justified on the basis of this small increment in the postmature baby."

*Presented at a meeting of the Pittsburgh Obstetrical and Gynecological Society, Oct. 6, 1952.

TABLE I. DATA FOR PATIENTS MORE THAN 14 DAYS POSTMATURE

PATIENT	AGE (YEARS)	PARITY	DAYS OVERDUE	HOURS OF LABOR	TYPE OF DELIVERY*	WEIGHT OF INFANT	SEX OF INFANT
1	29	iv	22	4	S	10- 4	m
2	27	i	19	2	S	8- 2	f
3	21	0	17	2	S	4- 9	f
4	26	i	20	2	S	7-10	f
5	24	0	18	18	M	7- 5	f
6	19	0	26	18	L	7-11	f
7	27	ii	17	10	S	8-11	m
8	32	0	15	24	M	8- 0	m
9	21	0	17	24	M	6-10	m
10	30	i	15	6	S	9- 3	m
11	32	ii	21	4	S	9- 6	m
12	25	i	26	4	S	7- 8	m
13	29	ii	28	4	S	6-15	f
14	25	0	19	8	S	8- 8	m
15	22	i	17	4	L	10- 4	m
16	22	ii	32	6	S	8-13	m
17	33	ii	35	6	S	8-10	m
18	27	0	18	12	B	8- 5	f
19	20	0	21	12	L	7- 0	f
20	21	i	35	6	S	9- 9	m
21	23	0	19	8	L	7- 0	f
22	21	i	22	12	L	9-11	m
23	21	0	14	8	S	8- 1	f
24	25	0	15	12	S	6- 1	f
25	30	ii	15	2	S	7- 4	f
26	28	i	23	4	S	6-10	m
27	36	vii	16	4	S	8- 0	f
28	19	0	24	24	L	8-13	m
29	23	0	45	18	L	7-11	m
30	24	0	14	14	L	8- 6	m
31	36	ii	20	4	S	7- 0	f
32	26	i	20	4	S	8-12	f
33	29	ii	45	4	S	9- 3	f
34	25	0	17	12	L	7-10	m
35	28	i	19	6	S	8-15	f
36	31	iii	18	8	S	7-15	f
37	26	0	33	8	L	6-12	m
38	29	0	21	8	B	7- 9	m
39	31	i	32	4	S	7- 4	f
40	30	0	23	12	L	6-14	m
41	25	i	19	6	S	6-11	f
42	27	0	17	6	L	8- 2	f
43	26	i	15	6	S	6-12	m
44	25	0	20	18	L	7- 0	f
45	24	0	15	8	L	8- 3	m
46	23	0	15	12	L	6- 4	f
47	31	i	26	6	S	6-14	m
48	22	0	25	12	L	6-13	m
49	17	0	23	12	L	8- 7	f
50	27	i	30	4	S	7-15	m
51	20	0	40	18	L	7- 7	m
52	27	i	15	4	S	7- 3	m
53	23	0	27	12	L	8- 4	f
54	20	0	30	24	M	8-12	f
55	20	0	20	8	L	6-13	m†

TABLE I—CONT'D

PATIENT	AGE (YEARS)	PARITY	DAYS OVERDUE	HOURS OF LABOR	TYPE OF DELIVERY*	WEIGHT OF INFANT	SEX OF INFANT
56	27	ii	16	4	S	8- 4	f
57	23	i	21	3	S	9-11	m
58	27	i	14	4	S	9- 2	m
59	31	0	14	8	L	7-12	f
60	16	0	18	6	L	7- 0	f
61	34	i	14	6	S	6- 7	m
62	23	0	37	12	L	7- 1	m
63	22	i	15	10	L	6- 3	f
64	23	i	22	4	S	7-11	m
65	29	i	15	6	S	6- 7	f
66	19	0	14	8	L	7-15	f
67	20	i	19	6	S	7- 0	f
68	27	i	15	6	S	8-10	f
69	22	i	26	12	S	7- 2	f
70	24	ii	20	6	S	4- 0	f†
71	28	i	45	6	S	8- 0	f

*S, spontaneous delivery; L, low forceps delivery; M, midforceps delivery.
†Stillborn infant.

TABLE II. LARGE BABIES (OVER 9 POUNDS OR 4,000 GRAMS), 9 CASES

PATIENT	DAYS OVERDUE	HOURS OF LABOR	TYPE OF DELIVERY	WEIGHT OF INFANT
1	22+	4	Spontaneous	10 pounds, 4 ounces
15	17+	4	Low forceps	10 pounds, 4 ounces
22	22	12	Low forceps	9 pounds, 11 ounces
57	21	3	Spontaneous	9 pounds, 11 ounces
20	35	6	Spontaneous	9 pounds, 9 ounces
11	21+	4	Spontaneous	9 pounds, 6 ounces
33	45	4	Spontaneous	9 pounds, 3 ounces
10	15	6	Spontaneous	9 pounds, 3 ounces
58	14	4	Spontaneous	9 pounds, 2 ounces

TABLE III. LONG LABORS (OVER 12 HOURS), 10 CASES, ALL PRIMIGRAVIDAS

PATIENT	DAYS OVERDUE	HOURS OF LABOR	TYPE OF DELIVERY	WEIGHT OF INFANT
5	18+	18	Midforceps	7 pounds, 5 ounces
6	26	18	Low forceps	7 pounds, 11 ounces
8	15	24	Midforceps	8 pounds, 0 ounces
9	17	24	Midforceps	6 pounds, 10 ounces
28	24	24	Low forceps	7 pounds, 11 ounces
29	45+	18	Low forceps	7 pounds, 11 ounces
37	33	36	Low forceps	6 pounds, 12 ounces
44	20	18	Low forceps	7 pounds, 0 ounces
51	40	18	Low forceps	7 pounds, 7 ounces
54	30	24	Midforceps	8 pounds, 12 ounces

The second problem: Does postmaturity increase the length of the labor? The average labor of this entire series was a little more than eight hours. Only 10 patients had labors longer than twelve hours. All were primigravidas and included some with malpresentations requiring forceps rotation. The weights of these infants were not remarkable and it is doubtful that postmaturity could have been a factor in these labors.

Data on the delivery of these patients show that there were 40 spontaneous deliveries, 25 low forceps deliveries, 4 midforceps, 2 breech extractions, and no cesarean sections.

There were two stillborn infants and no neonatal deaths.

Patient No. 55, aged 20 years, para o, 20 days overdue, had an eight-hour labor, was given 3 grains of Seconal and 40 mg. Nisentil, and saddle-block anesthesia for delivery, with central episiotomy and outlet forceps, of a stillborn male infant weighing 6 pounds, 13 ounces. This infant died some time during labor. There was a questionable partial premature separation of the placenta.

Patient No. 70 was a 24-year-old, para ii, 20 days overdue, who had a six-hour labor, was given Seconal and inhalation anesthesia, and was delivered spontaneously of a stillborn female infant with anencephaly and spina bifida, who weighed four pounds.

Conclusion

Postmaturity is not a dangerous complication to the mother of the fetus. Postmaturity does not produce excessively large babies nor lead to an increase in the average length of labor. It is not an indication for cesarean section.

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EXPERIENCES WITH HYDATIDIFORM MOLE AND CHORIONEPITHELIOMA*

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WHILE hydropic change in the chorionic villus is the characteristic which leads to the diagnosis of hydatidiform mole, the significant and common change in both mole and chorionepithelioma is some, though variable, degree of trophoblastic proliferation. This proliferating trophoblast is always potentially malignant but the degree of malignancy is one about which qualified pathologists do not agree. This review of a small series of these cases is undertaken in an effort to evaluate and perhaps systematize our therapy of these patients.

During the past 12 years, 13 cases of mole or chorionepithelioma were seen. Of these, 7 moles occurred in our own practices in approximately 4,320 pregnancies giving an incidence of 1 in 617 pregnancies, which is a greater incidence than is usually found in the literature where it is variably given between 1 in 1,500 and 1 in 3,000.

We cannot from this series compute any incidence of chorionepithelioma as the 6 cases so classified were all referred and thus represent the unusual cases in an indefinitely large number of pregnancies.

We must define the varieties of chorionepithelioma as that term is used in this report. These based on Ewing's classification, adapted from Hertig,[1] are as follows: Syncytial endometritis is characterized clinically by variable amounts of uterine subinvolution, postpregnancy bleeding, and persistently positive tests for chorionic gonadotropic hormone, pathologically by accentuation of the placental site giant cells plus chronic infection. It is considered of questionable malignancy. Chorioadenoma destruens is characterized clinically by the same triad of findings but pathologically by myometrial invasion by low-grade malignant trophoblast usually still associated with villi. Choriocarcinoma is characterized clinically as an extremely fatal chorionic malignancy that may follow any type of pregnancy but most commonly mole; pathologically by metastases commonly to lungs, brain, and vagina. Residual tissue may or may not be found in the uterus which classically is not enlarged. These metastases are pure chorionic epithelium without other villous elements.

By these criteria our 13 cases are classified as follows: benign hydatidiform mole 6, syncytial endometritis 2, chorioadenoma destruens 4, and choriocarcinoma 1 (probable).

Case Reports

A summary of the simple benign moles is seen in Table I. The remaining 7 cases are summarized individually somewhat more fully:

*Presented at the Fourth Annual Meeting of the Pacific Northwest Obstetrical and Gynecological Association, Glacier Park, June 25 to 28, 1952.

CASE 1.—(1947) L. I. N., a 24-years-old para ii, delivered at term, was admitted because of hemorrhage on the twelfth postpartum day. This was treated by oxytocics and transfusions only. At the 6 weeks post partum examination the uterus was reportedly "well involuted." From the third month on the patient bled intermittently and hemorrhaged severely 6½ months post partum so curettage was done. "The cervix was open. A large amount of tissue was obtained" which was diagnosed locally as "choriocarcinoma." The Friedman test and x-ray of the chest were negative. Slides were submitted after the curettage to Drs. Novak and Hertig, who were agreed on the diagnosis of "choriocarcinoma" and advised total hysterectomy with bilateral salpingo-oophorectomy. She was now seen for the first time by one of us, who performed the advised operation 7 months post partum. The pathologist on studying the uterus now reported "small choriocarcinoma in placental polyp." These sections were again submitted to Drs. Novak and Hertig, who again agreed on the diagnosis as "placental polyp with syncytial endometritis." This patient is alive and well 5 years later.

CASE 2.—(1946) P. E. T., a 42-year-old para 0, gave a history of menometrorrhagia. The onset of bleeding occurred when she was 3 days past her first missed period, and continued 1 month, when a diagnostic curettage was done. The pathologist reported "chorionepithelioma" because of trophoblastic invasion of the myometrium apparent even in the curettings. An immediate Friedman test was questionably positive. A total hysterectomy with bilateral salpingo-oophorectomy was done. The uterus was not enlarged and there was but slight questionable invasion of the myometrium. The diagnosis now was syncytial endometritis. The patient's course has been uneventful for 5 years.

CASE 3.—(1947) H. S., a 22-year-old gravida i, had spotted at each missed menstrual time until the seventh month when, the uterus being of a size still consistent with dates, molar tissue was expelled. A finger curettage was done. Bleeding continued intermittently for 2½ months when a supracervical hysterectomy was performed. The uterus was reported negative by the pathologist. One month later the patient began to flow heavily. This gradually decreased to a mild mucosanguineous discharge when, because of a positive Friedman test (her first), she was referred for radiation therapy. The radiologist referred the patient to one of us, who excised a grossly distended cervix with 2 areas of invasive tissue, without villous structures, in its wall. The pathologist reported "chorionepithelioma." Dr. Hertig classified the invasive tissue as probably choriocarcinoma and Dr. Novak classified it as "either a chorionepithelioma or chorioadenoma destruens"—the absence of any villous structures in the invasive tissue being the pivotal factor. X-rays were negative. Following surgery radiation therapy was given the patient. Her Friedman tests have been persistently negative and she is well 5 years postoperatively.

CASE 4.—(1946) J. McR., a 22-year-old gravida iv, para ii, began bleeding when 3 days past the expected menstrual date. This persisted in variable degree until the patient was hospitalized at 3 months (menstrual age). The fundus was noted to be "two finger-breadths below the umbilicus." Molar tissue was passed on admission. Immediate curettage was done. She was discharged without transfusion though the hemoglobin was only 8.5 Gm. The pathologist diagnosed "chorionepithelioma" on molar tissue only. The bleeding continued and the patient was first seen in consultation approximately 2 months after passage of the mole. The Friedman test was positive in diluted serum, the uterus was of a size consistent with an 8 weeks' pregnancy, the hemoglobin was 6.0 Gm. Transfusions were given and total hysterectomy with left salpingo-oophorectomy (the latter because of adhesions to the uterus) was done. The pathologist now reported invasive mole (villi in association with invasive trophoblastic tissue in 2 intramyometrial nodules). Repeated Friedman tests were negative and the patient is alive and well 3½ years later. The Mathieu Registry has always classified this as a chorioadenoma destruens.

CASE 5.—(1949) P. E. R., a 39-year-old woman, began bleeding at her normal menstrual time, never having missed a period. The flow was heavy for 2 days, then intermittent for 5 weeks, when on examination the uterine fundus was "3 cm. below the umbilicus, the

TABLE I

CASE AND YEAR	AGE (YEARS)	GRAVIDA	PARA	DIAGNOSIS PRIOR TO "CYSTS"	MONTH CYSTS PASSED	UTERINE SIZE IN MONTHS	BLEEDING	NAUSEA	EMESIS	PAIN	FRIEDMAN TEST	TREATMENT	LATER COURSE
A. M. 1941	26	i	0	Missed abortion	4½	2½ (small)	+	0	–	0	++ preoperatively – fourth postoperative day	Curettage; repeated Friedman	Uneventful, 4 full-term deliveries
G. M. 1942	22	i	0	Inevitable abortion	3½	2½ (small)	+	+	–	+–	– postoperatively	Same	Uneventful, 2 full-term deliveries
M. S. 1947	20	ii	i	Inevitable abortion	3	"small"	++	0		0	– day of operation	Same	Uneventful
M. C. 1949	31	iv	iii	? Mole or intrauterine bleeding	2½	3½ (large)	++	+	–	0	– 2 weeks postoperatively	Same. Transfused	Uneventful
P. P. 1951	24	ii	i	Spontaneous abortion	3½	? slt. small	+	+	–	+–	+ day of operation – 2 weeks postoperatively	Same	Now pregnant
J. H. 1952	24	ii	i	Inevitable abortion	2	3 (large)	+	+	+	++	+ fifth postoperative day – fourteenth postoperative day	Same	Uneventful to date

Note.—None of these patients exhibited any symptoms of "premature toxemia."

cervix was dilated and molar tissue was being extruded.'' Immediate dilatation and curettage were done. Profuse hemorrhage recurred 24 days later and the patient was first seen in consultation. The Friedman test was strongly positive in diluted serum, the uterus was consistent with an 8 weeks' pregnancy, the left ovary was cystic. Total hysterectomy was done. A fungating mass filled the uterus and there was trophoblastic invasion of the myometrium. The diagnosis was chorioadenoma destruens (Mathieu Registry). The postoperative course has been uneventful to date.

CASE 6.—(1951) P. H., a 27-year-old gravida iv, para iii, was first seen at the second missed menses because of severe nausea which was unusual for this patient. The uterus was of a size consistent with dates. The usual treatment was instituted. Nausea and vomiting increased, backache became a prominent symptom, and 2 weeks later spotting was noted. Now on examination the size of the uterus was consistent with a 3 months' gestation. One week later the size of uterus was consistent with a 4 months' gestation bleeding had ceased, but both ovaries were cystic, 6 to 8 cm. in diameter. The Aschheim-Zondek test was begun in dilutions. The next day bleeding was profuse but the cervix was still closed and the flow was controlled. Five days later the Aschheim-Zondek was reported positive in 1:1,000 dilution. Dressing forceps were used to pull molar tissue from the uterus confirming the diagnosis, and total hysterectomy was done. The lutein cyst of the ovaries were aspirated but not removed. X-rays were negative. The pathologist reported chorioadenoma destruens. The first test 16 days postoperatively was positive only in undiluted serum; since then repeated Aschheim-Zondek tests have been negative. The patient is apparently well to date.

CASE 7.—(1950) D. U. D., a 50-year-old para ix, gave an uncertain menstrual history but had irregularly profuse bleeding of 3 months' duration. A dilatation and curettage were done and molar tissue found. The pathologist questioned the malignant nature of this tissue. Hysterectomy was advised but refused. Three weeks later intermittent spotting began and continued for 2 months when bleeding became profuse and the patient was first seen in consultation. The Friedman test was positive in dilutions. Chest x-ray was negative. The uterus was the size of an 8 to 10 weeks' pregnancy. Total hysterectomy and bilateral salpingo-oophorectomy were done. The uterus was filled with a massive clot attached to a gray-pink nodule of tissue invading the myometrium. A similar nodule was found in the opposite wall. These were diagnosed chorionepithelioma. The patient refused further study or treatment. Six months later she developed convulsions, was readmitted in coma, and died 48 hours later. No autopsy could be obtained.

Diagnosis: Probably choriocarcinoma with cerebral metastases.

Comment

The diagnosis of hydatidiform mole was considered only 3 times prior to extrusion of molar tissue in the cases of benign mole. We think it should have been considered more frequently in the differential diagnosis. Bleeding was the constant symptom. Rapid growth and excessive size of the uterus especially, despite bleeding, are suggestive when they occur; 6 of the 11 moles discussed here were associated with this sign. Excessive nausea and vomiting, disproportionate pain, backache, and ''premature'' toxemic symptoms are all suggestive but not so prominent in this series. The presence of bilateral cysts of the ovaries which occurred twice is almost pathognomonic. The finding of hydropic villi, of course, confirms the diagnosis.

In this regard we believe that all abortuses should be inspected grossly to rule out molar degeneration. If, however, the hydropic change in the villi requires microscopic examination for diagnosis it seems probable that no other than ordinary care of the abortion is necessary.

The diagnosis of chorionepithelioma is facilitated in like manner by always being considered as a possibility. Especially following mole are we always on the alert, for it has been established that approximately 50 per cent of chorion-

epithelioma follows mole or, conversely, that 1 to 5 per cent of moles are followed by malignancy. We should be equally alert when abnormal bleeding follows normal or ectopic pregnancy, each of which precedes approximately 25 per cent of chorionepitheliomas. But here bleeding may not be so significant as a persistent and increasingly positive test for chorionic gonadotropin. A failure to consider chorionepithelioma in the differential diagnosis may well be a factor in the delay in diagnosis and treatment of those cases following normal and ectopic pregnancy and may account, at least in part, for the apparently greater degree of malignancy characterizing such cases.

Each of our cases of chorionepithelioma exhibited one or more of those signs and symptoms suggestive of malignancy following pregnancy—bleeding, persistently positive Aschheim-Zondek test, subinvolution. Most were seen in consultation some time after the onset of symptoms. In one case the original curettage, being limited to finger curettage, may be assumed to have been incomplete. We suspect this to have been true in at least 2 others. This leads us to wonder whether more thorough initial treatment would have changed the later course in these patients, or whether the trophoblast had been locally malignant from its inception.

We are impressed with the tendency of the pathologists to diagnose malignancy—usually of a high degree—after study of the curettage specimens in these cases. After study of the hysterectomy specimens the malignancy was judged of lesser degree, though the local malignancy was still a valid reason for the surgery done. There is in this regard considerable confusion in terminology—to some chorionepithelioma connotes choriocarcinoma, to others it means any of the triad: syncytial endometritis, chorioadenoma destruens, or choriocarcinoma.

The treatment of these cases consisted in every case of removal of all, or the remaining part, of the uterus. Salpingo-oophorectomy was done bilaterally in 2 cases where the patients were more than 40 years of age, bilaterally in one case at the behest of the referring physician and pathologist, and unilaterally in one case because of adhesions involving these organs. Postoperative irradiation was used in one case by the referring radiologist. It would appear to us that not all were necessary because of the disease process, as metastasis to the ovary is so uncommon in this condition. However, where the ovary is involved in the growth it should be widely removed, and we will not cavil at the castration of the premenopausal patient in this situation.

The initial treatment of hydatidiform mole offers little problem—evacuation of the uterine contents and curettage are generally accepted. In our opinion hysterotomy offers little if any advantage in this regard and several possible disadvantages: (1) spill into the peritoneal cavity, (2) a false sense of complete inspection unless the uterus is completely bivalved, and (3) a probable dependence on cesarean section in subsequent deliveries. An immediate base-line quantitative test for chorionic gonadotropin should be done and the patient followed with monthly tests for 6 months, then every 2 months until the end of a year. The test should be negative within 2 months and continue so.

But what of persistent bleeding and/or a persistent and rising titer of chorionic gonadotropin. Malignant change is diagnosed on (1) chorionic gonadotropin titer rise, (2) the curettings, and (3) the clinical findings—especially bleeding with varying amounts of subinvolution, and evidence of metastases by x-ray or neurological study.[2]

No hidebound dicta can be laid down as cases must be individualized but we believe the following generalities should apply:

1. Intervening pregnancy should be ruled out so far as possible. Chorionic gonadotropin of normal pregnancy reaches a peak at 1 month—a later rise suggests chorionepithelioma.

2. Unless there is a desire for future childbearing total hysterectomy should be done without delay.

3. If future childbearing is desired a repeat curettage and Aschheim-Zondek test may be done but if the titer is still rising, after apparently complete evacuation of the uterus, hysterectomy is the procedure of choice. The removed uterus will not, in most cases, reveal choriocarcinoma but will show residual hydropic villi, often with marked trophoblastic proliferation, deep in the maternal vessels or myometrium where they are inaccessible to the currette. Or one will be made even more aware of the limitations of curettage by finding superficially attached villi or a placental polyp missed by the curette as in one of the cases of syncytial endometritis reviewed above. As a general rule a negative curettage in the presence of a long-persistent or rising titer should be assumed to mean local penetration of the myometrium, or distant metastasis. Lutein cysts may cause a persistent but usually decreasing titer.

4. Such metastases must be sought in the lungs, brain, vagina, liver, and kidneys. X-ray and neurologic studies are most important, together with a thorough gynecologic review.

5. Even in the presence of distant metastases hysterectomy should be done, as metastases have been known to disappear and have in one case reported by Maier and Taylor[3] been successfully treated by a direct surgical approach. This is in direct contrast to the advice of de Alvarez[4] who advocated only radiation therapy in the presence of metastases.

6. In view of our own experience we disagree with Holman's[5] statement that the hysterectomy may be total or subtotal, as we believe hysterectomy should be total in type.

7. We agree with Holman, however, that the ovaries need not be removed unless involved in the tumor growth. Many disagree with this.[2, 4]

8. We have had no experience on which to judge the efficacy of radiation therapy. Holman would limit its use to the treatment of metastases and we are inclined toward this view.

Adherence to this proposed outline of therapy might lead to the removal of some uteri—we believe justifiably—in the presence of possibly benign lesions—i.e., syncytial endometritis and invasive mole. Numerous cases are reported in the literature[1, 6] in which patients for various reasons have not been subjected to surgery and have survived many years. While it is possible for the local trophoblastic tissue to regress—even as do metastases which characterize the most malignant form—it is our belief that one should not place so great a dependence on spontaneous regression, that early surgery will obviate the risk of death by perforation, hemorrhage, and sepsis in the case of chorioadenoma destruens, and help decrease the admittedly low incidence of fatal choriocarcinoma.

Such belief is based on two assumptions: (1) that the differentiation of chorionepithelioma into its major divisions is an artificial one, there being many cases which cannot be strictly classified as belonging to a specific group (in this regard we agree with Holman that a better classification would be choriocarcinoma, Grades I to IV, evidencing the significant common factor of trophoblastic proliferation); and (2) that choriocarcinoma is at some early stage a curable disease. It does not seem logical to require death as a diagnostic criterion—surely some local growths are removed just prior to metastasis. In this regard Jeffreys'[7] recommendation of dilatation and curettage in all abortions may be worth while as a prophylactic measure.

Summary and Conclusions

1. Our experience with 13 cases of mole and chorionepithelioma is briefly reviewed.

2. No matter how benign appearing the mole, all patients should have a complete follow-up—decreasing titers of chorionic gonadotropin permit watchful waiting, any increase must be evaluated as a recurrent pregnancy or malignancy.

3. Chorionepithelioma should be considered whenever abnormal bleeding or a persistently positive test for chorionic gonadotropin is found after pregnancy of any kind.

4. The degree of malignancy in these cases cannot be judged on curettings alone.

5. In the presence of a rising titer of chorionic gonadotropin and the presumption of chorionepithelioma, hysterectomy is advisable.

6. We agree with Holman that the terminology of chorioma should be clarified.

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UTERINE ARTERIOVENOUS FISTULA

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THE occurrence of an arteriovenous fistula within the uterus is a rarity. It may be productive of profound circulatory changes and severe uterine bleeding. The clinical findings are sufficiently characteristic to suggest the correct diagnosis, provided the possibility of its existence is borne in mind. A review of the literature has revealed only three cases[1, 2, 3] similar to the one to be described in this paper. A comparative analysis of their essential features will be made below.

Before discussing uterine arteriovenous fistulas, it may be proper to summarize the status of similar vascular shunts elsewhere in the body. A variety of terms have been applied to these lesions, often depending upon their superficial appearance. These include: arteriovenous aneurysm, cirsoid aneurysm, pulsating angioma, cavernous angioma, etc. An arteriovenous fistula, however, is the basic pathologic feature.

Arteriovenous fistulas may be of congenital or acquired origin. The congenital group presumably results from the failure of differentiation of the common embryologic anlage into definitive artery and vein, with the resultant persistence of anastomotic channels between arterial and venous trunks. The sites of predilection for congenital lesions are the scalp, intracranial region, neck, and extremities. Visceral lesions have also been described within the lungs, stomach, duodenum, pancreas, spleen and kidney.[4] In the congenital type, many years may pass before clinical manifestations become evident. A history of trauma is not obtained. Usually, multiple small fistulas are present within the area involved.

An acquired arteriovenous fistula is usually single. It may follow trauma with a blunt instrument, penetrating wounds, or operative procedures. The mass ligation of arteries and veins, or the transfixtion and ligation of vessels have been said to result, on occasion, in a fistulous communication. A case in point is that reported by Elkin and Banner[5] in which an arteriovenous fistula of the right uterine artery and vein was found and removed five months after a routine hysterectomy. Presumably, this had been caused by needle penetration of contigous artery and vein during the suture ligation of the uterine vessels.

The presence of an abnormal direct communication between the arterial and venous circulation is usually associated with clinically significant local, and occasional systemic, effects. Locally, a pulsating swelling may be evident. Especially characteristic is the presence of a palpable thrill and an audible bruit. With the stethoscope, a continuous murmur with systolic accentuation is heard. Because of the increased volume and pressure of arterial blood shunted through the fistulous opening, there are conspicuous dilatation and tortuosity of the veins proximal and distal to the fistula. The artery proximal to the fistula is usually dilated. The collateral vessels, both venous and arterial, are increased in size. Signs of increased venous pressure may be evident in the early stages.

The systemic manifestations are particularly influenced by the size, location, and duration of the arteriovenous fistula. In the majority of cases, the basal cardiac output will show an elevation above that found after operative removal of the fistula. It has been suggested that this increase in cardiac output is the best evidence of the functional size of the fistula. The pulse pressure is often increased, due especially to the fall in the diastolic pressure. The heart rate may be normal or slightly elevated. The heart itself may show slight dilatation. In the presence of a sizable fistula, the blood volume may be increased. Systemic venous pressure is usually normal except in the presence of cardiac insufficiency. Frank congestive heart failure may occur with large fistulas of long standing.

Wherever possible, therapy is directed at the surgical removal of the arteriovenous fistula. At times, this may be a hazardous procedure.

Case Report

Mrs. S. J., a 58-year-old white housewife, was first admitted to the Gynecological Service of The Mount Sinai Hospital in August, 1951, because of postmenopausal bleeding of two weeks' duration. She had been pregnant seven times and had given birth to four full-term, normal infants. Thirteen years before, at the age of forty-five, a dilatation and curettage of the uterus had been performed for menorrhagia. One menstrual period was noted soon after this procedure. Vaginal bleeding did not recur thereafter until the onset of the present illness. The patient had been aware of hypertension for eight years and had also been told that she had "gall-bladder disease." Slight exertional dyspnea after moderate exercise, and frequent headaches had been present for many months.

Physical examination revealed a well-developed, obese woman in no acute distress. The temperature and respirations were normal. The pulse rate was increased slightly to 90 per minute. Examination of the head, neck, and chest was essentially negative. The blood pressure was 195/95. The heart presented a regular sinus rhythm. The point of maximum impulse was found in the fourth intercostal space, 2 cm. lateral to the left midclavicular line. A soft, systolic murmur was best heard at the apex. A_2 was greater than P_2. The abdomen was soft and nontender. The lower extremities revealed bilateral varicose veins of slight degree, normal peripheral pulsations, and no evidence of edema.

On pelvic examination the external genitals were normal in appearance. The perineum was moderately relaxed. A small amount of dark blood was evident in the vagina. The cervix was clean, soft, and almost flush with the vaginal vault. The uterus was found to be symmetrically enlarged to the size of a three months' gravidity, globular in shape and slightly mobile. Its consistency was soft, resembling that of an intrauterine pregnancy. A conspicuous pulsation, synchronous with the heartbeat, could be felt in both lateral fornices. A distinct thrill was also noted in these areas.

Laboratory Examinations.—The blood count, erythrocyte sedimentation rate, urinalysis, blood Wassermann test and fasting blood sugar determination were found to be within normal limits. X-ray of the chest revealed a slight enlargement of the heart in its transverse diameter. Because of the history of mild exertional dyspnea and hypertension, venous pressures were determined in the upper extremities as well as the ether and Decholin circulation times. These were found to be normal.

Operation.—A preliminary diagnostic curettage was performed. The uterine cavity could be sounded for a distance of 5½ inches (14 cm.). The soft cervix was easily dilated, followed by the escape of a moderate amount of fresh blood and several large clots. On curettage, the uterine cavity was found to be distended by large blood clots. Bleeding was moderate. No endometrium could be obtained from the smooth lining of the soft uterine wall. In the presence of persistent bleeding and unexplained uterine pathology, an exploratory laparotomy was deemed advisable.

A left hypogastric, paramedian incision was made. The uterus was found to be congested and symmetrically enlarged to the size of a grapefruit. Large, pulsating, tortuous

vessels filled the broad ligaments. Dilated vessels were also noted in the infundibulopelvic ligaments. A total hysterectomy and bilateral salpingo-oophorectomy were done. Some difficulty was experienced in securing hemostasis, particularly about the cervix. Two units of blood were administered during the operation.

Postoperatively, an irregular rise in temperature persisted for several days, apparently due to the development of a moderate pelvic exudate. This was thought to have been initiated by a small, retroperitoneal hematoma probably secondary to incomplete hemostasis within the broad ligaments and parametrial regions. Blood count, hematocrit, platelet count, bleeding time, clotting time, and clot retraction determinations done on the second postoperative day were normal. At discharge on the eighteenth postoperative day, a small exudate was still present about the vaginal vault.

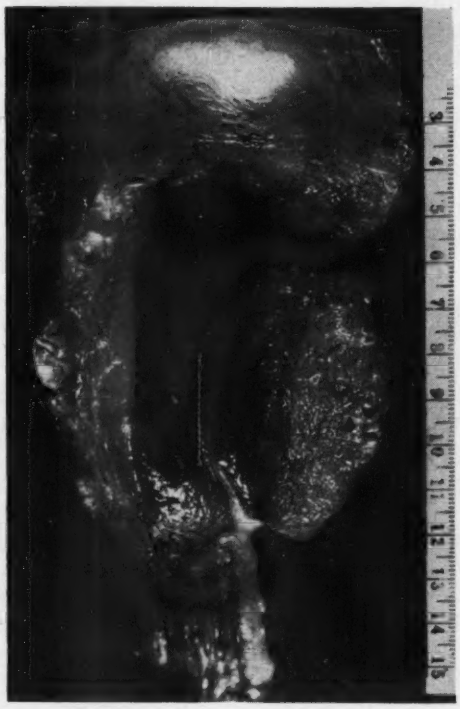

Fig. 1.—Hypertrophic, distended, and highly vascular uterus, secondary to arteriovenous fistulous communication within its wall. The general appearance resembles that of a gravid uterus. Within the myometrium, the vessels are conspicuously enlarged and numerous.

Gross Pathology.—The specimen included a totally resected uterus and both adnexa. The uterus (Fig. 1) was globular, and symmetrically enlarged to the size of a three months' gravidity. It measured approximately 15 by 10 by 6 cm. The serosal surface was smooth and congested. On palpation, the uterus was soft, with flabby walls, conforming to that seen in an intrauterine pregnancy. The open specimen revealed an enlarged, distended endometrial cavity measuring 12 cm. in length and 5.5 cm. transversely across the fundus. The cervical canal made up one-fourth the length of the entire uterus. The endometrium appeared smooth and atrophic. The myometrium averaged 3 cm. in thickness and had a rubbery consistency. Within the myometrium, especially in the lateral walls, the vessels were conspicuously enlarged and numerous. On section, in some areas, these grossly suggested sinuses. One uterine vessel near the isthmus was large enough to admit the tip of the fifth finger, approximating 1 cm. in diameter. The tubes and ovaries did not present any significant findings.

Microscopic Examination.—The adnexa showed no unusual features. The ovaries presented the typical atrophic changes associated with physiologic senility. A few scattered,

minute surface papillomas were seen. The Fallopian tubes showed increased fibrosis. The endometrium was thin, with sparse, inactive stroma and glands. The myometrium showed evidence of irregular fibrosis. Numerous sections taken through the more vascular portions of the uterus were stained with both hematoxylin and eosin, and with van Gieson's elastica stain. The vessels, many of which were of large size, might be divided into three categories; (1) those obviously arterial, with complete and heavy internal elastic membrane, (2) venous channels, and (3) a mixed variety. Some of the vessels in the last group suggested a combined arteriovenous channel, one section of which was composed of arterial wall, and the remainder of venous wall.

The arteries were of varying caliber and seemed to predominate. Several were straight, with thick even walls. Others appeared irregular in outline and of varying thickness. Here and there within the intima, localized moundlike or nodular thickenings might be seen, projecting conspicuously into the lumen. They consisted chiefly of fibrous tissue, some smooth muscle, and occasional elastic fibers. In several of the smaller vessels, these intimal changes had reduced the lumen to a narrow slit. The media appeared thickened and was composed of smooth muscle with small amounts of connective tissue and thin elastic strands. The external elastic membrane was fragmentary. There was no evidence of infection, cellular infiltration, calcium deposits, or hyaline degeneration.

The veins were dilated and frequently distorted. Fibrous intimal plaques were noted. The media appeared fibrous and rather thick.

Fig. 2.—Low-power magnification of a combined arteriovenous channel. One-third of the vessel circumference (*A*) shows typical arterial wall; while the remaining circumference (*B*) presents characteristic features of venous wall. *C* marks points of junction between arterial and venous walls.

Two vessels were seen which were not uniformly differentiated. One of these (Fig. 2) warrants a detailed description. It appeared large, irregular, and collapsed. One-third of its circumference was occupied by typical arterial wall (Fig. 2, *A*), while the remaining circumference presented features characteristic of venous wall (Fig. 2, *B*). The two points of junction (Fig. 2, *C*) between arterial and venous wall, though not sharp, were readily apparent under low-power magnification. In the junction areas, the vessel wall was composed almost exclusively of dense fibrous tissue. In the arterial portion (Fig. 3), a thickened, clearly defined internal elastic membrane, and a well-developed muscular media were seen. In the venous segment of the vessel wall (Fig. 4), the internal elastic layer occurred irregularly and was less distinct. The media was more fibrous and relatively thinner. A striking feature of the venous portion was its lack of uniformity, some areas being better

developed than others. Intimal thickening and nodules were noted throughout the vessel. Within the same slide, another smaller vessel presented a similar composite picture, one-half being arterial and the other half suggesting venous wall.

After thorough study, the Division of Pathology reported: Hypertrophic uterus showing arteriovenous fistula and areas of fibrosis.

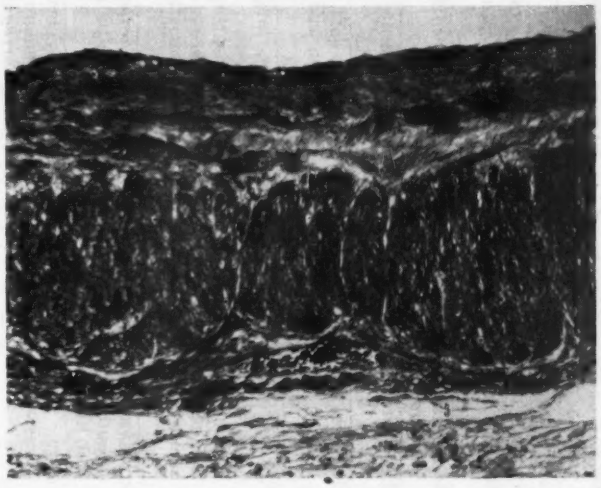

Fig. 3.—High-power magnification of the arterial portion of the combined arteriovenous channel (Fig. 2, *A*). Beneath the thickened intima, a well-developed muscular media is seen. A clearly defined internal elastic membrane was evident with van Gieson's elastica stain. (Hematoxylin and eosin stain.)

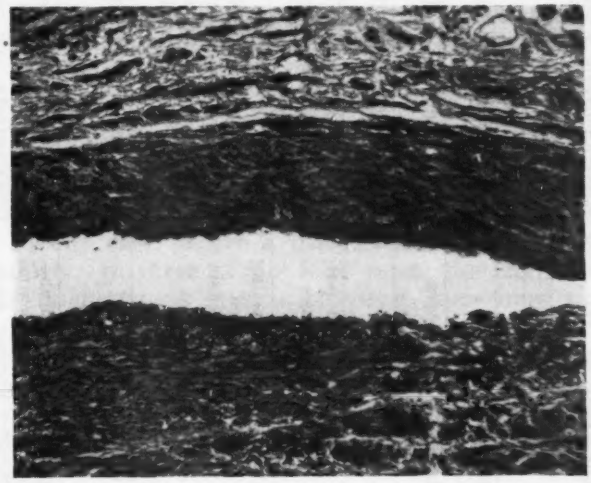

Fig. 4.—High-power magnification of the venous portion of the combined arteriovenous channel (Fig. 2, *B*). The media is fibrous and thin. With van Gieson's elastica stain, the internal elastic membrane was found to be fragmentary and indistinct. (Hematoxylin and eosin stain.)

Follow-up examination nine weeks after discharge revealed the patient to be in good health. A small residual thickening was still palpable above the vaginal vault. In the left parametrial area, a definite pulsation could be felt, synchronous with and similar to the radial pulse. In February, 1952, five and one-half months after operation, the patient was readmitted for evaluation of her circulatory status. It was desired to determine whether any residual arteriovenous communication existed within the pelvis. The patient stated that she

TABLE I. COMPARATIVE FINDINGS IN THE REPORTED CASES OF UTERINE ARTERIOVENOUS COMMUNICATIONS

	1. DUBREUIL AND LOUBAT, 1926	2. GRAVES AND SMITH, 1927	3. REYNOLDS, OWEN AND CANTOR, 1949	4. GAINES AND GREENWALD
Diagnosis	Cirsoid aneursym of the uterus	Cirsoid aneursym of the uterus	Arteriovenous aneursym of uterine artery and vein	Uterine arteriovenous fistula
Age of patient	62 years	62 years	42 years	58 years
Parity	Para iv	Gravida v, para iv	Gravida ii, para i	Gravida vii, para iv
Menstrual status	9 years postmenopausal	14 years postmenopausal	Regular menses	13 years postmenopausal
Chief complaint	Uterine bleeding 1½ years	Profuse uterine bleeding 3 weeks	Menstrual headaches; right leg numbness	Uterine bleeding 2 weeks
General	Anemia	Anemia; blood pressure 160/80	Blood pressure 120/50	Blood pressure 195/95
Pelvic examination	Enlarged uterus; vaginal pulsation; uterine bleeding	Pulsations in vaginal fornices; uterine bleeding	Enlarged, soft uterus	Enlarged, soft uterus; vaginal pulsation and thrill; uterine bleeding
Operative findings	Large, soft, spongy, pulsating uterus; thrill; engorged vessels; difficult hemostasis	Curettage followed by formidable hemorrhage; enlarged, spongy, pulsating uterus; varicosities of uterus and pampiniform plexus; difficult hemostasis	Curettage followed by profuse hemorrhage; large, soft uterus; tortuous vessels in the broad ligament; difficult hemostasis	Curettage, large clots; large, soft uterus; dilated, tortuous, pulsating varicosities of the broad ligament; difficult hemostasis
Operation	Supravaginal hysterectomy	Supravaginal hysterectomy	Supravaginal hysterectomy; secondary operation to control bleeding	Total hysterectomy and bilateral salpingo-oophorectomy
Micropathology	Hypertrophic vessels; differentiation between artery and vein difficult; fibrosis within myometrium	Irregular and variable vessel changes; differentiation between artery and vein difficult; fibrosis within myometrium	Large, heavy-walled vessels; fibrosis of myometrium	Dilated, hypertrophic vessels; arteriovenous communications; irregular fibrosis of the myometrium
Follow-up	Died 5 days after operation due to intestinal obstruction	Mild cerebrovascular accident postoperatively; well	Well	Well

felt very well. The headaches and exertional dyspnea were no longer present. On examination, the pelvis was felt to be clear, except for the normal peripheral type pulsation previously noted in the left parametrium at follow-up examination. The blood pressure was unchanged, namely, 195/95. Urinalysis, blood count, erythrocyte sedimentation rate, blood urea nitrogen, fasting blood sugar, venous pressures, and Decholin circulation time determinations were within normal limits. The basal metabolic rate was reported as plus 8 per cent. An observation cystoscopy revealed no dilatation of bladder vessels. The retinal vessels presented mild sclerosis. The electrocardiogram indicated hypertrophy of the left ventricle with involvement of the ventricular muscle. Microplethysmograms obtained from both great toes, as suggested by Goetz,[6] were normal in contour and amplitude. The tracings failed to evince any of the characteristic volume-pulse contour activations associated with extracardiac arteriovenous communications. Chest x-ray revealed essentially no change. Numerous oscillometric readings in both upper thighs, the lower thighs, and the mid-calves were within normal limits. Blood volume determination with P_{32} labelled red blood cells, according to the method of Berlin and associates,[7] was normal. The total blood volume was 3,875 c.c. With a hematocrit of 42 per cent and a body weight of 65.0 kilograms, the total red cell volume and plasma volume were determined to be 1,628 c.c. and 2,247 c.c., respectively.

From these studies, it is reasonable to assume that the arteriovenous fistula had existed entirely within the uterus and had been completely removed by total hysterectomy.

Comment

Table I summarizes the comparable data of the three cases reported in the literature, with our own. The terms, cirsoid aneurysm of the uterus and arteriovenous aneurysm of the uterine artery and vein, were used by the previous authors. Cirsoid means varicose, and refers to a characteristic, superficial racemose appearance. An aneurysm is basically a vascular dilatation. To avoid the confusion of a varied and essentially descriptive terminology, and in keeping with the desire to stress the basic pathology, which is an abnormal communication between artery and vein, we have preferred to use the term arteriovenous fistula.

This condition, as applied to the uterus, has been observed in three instances long past the menopause, at 58 and 62 years of age, and in one instance at 42 years of age. All of the patients had borne one or more children, apparently without undue bleeding or other significant complications. Previous pelvic surgery, which might be considered as a possible etiological factor, had been performed only in our case, where a dilatation and curettage had been done thirteen years before. In three of the four cases, the characteristic presenting complaint was postmenopausal uterine bleeding, sometimes profuse, and often associated with a secondary anemia. It is of interest that in arteriovenous fistulas of other visceral organs, mentioned by Adams,[4] hemorrhage was a common symptom. Aside from the local findings, the general physical examination was not significant. The hypertension noted in our case was regarded as coincidental. Evidence of circulatory changes related to cardiac embarrassment was not seen. That no cardiac failure occurred in the uterine series is not unexpected, in view of the report by Elkin and Warren[8] on 400 cases of traumatic arteriovenous fistulas. Frank cardiac failure was not found in any case, although many manifested increased cardiac output and blood volume.

Pelvic examination uniformly revealed the presence of an enlarged, soft uterus, resembling that of an intrauterine gravidity. In the only case which occurred during menstrual life, in the woman 42 years of age reported by Reynolds and collaborators,[3] the findings were characteristic enough to warrant a pregnancy test being done, despite the regular menstrual cycle. In the present case, the size of the uterus approached that of a three months' gravidity. The most significant finding was the presence of distinct pulsations in the vaginal

fornices, synchronous with the peripheral pulse beat, and associated with a palpable thrill. At operation, the gross findings were fairly uniform in all cases. The uterus was large and soft, sometimes with subserous varices. The vessels in the broad ligaments were conspicuously dilated, tortuous, and pulsating. A thrill was felt within the engorged vessels by Dubreuil and Loubat.[1] The resemblance of this picture to that of an advanced pregnancy is not surprising. During pregnancy a temporary but typical physiological arteriovenous shunt is present at the placental site. Arterial blood is forced through expanded, thin-walled sinuses into a placental lake. From there the return flow is carried into the uterine veins, without an intervening capillary system. As a result, marked engorgement and dilatation of the venous system occur within the uterus and broad ligaments, with characteristic uterine souffle and thrill.[9]

A preliminary dilatation and curettage of the uterus, performed in three of the four cases, initiated a formidable or profuse hemorrhage in two, and moderate bleeding with large clots in one. In view of the marked vascularity of the uterus, this is understandable. Hemostasis at the time of hysterectomy was found to be difficult in all instances. This is consistent with surgical experience for arteriovenous fistulas in general. In one instance, a secondary laparotomy to control bleeding was found necessary. In our case, where a total hysterectomy was done instead of a supracervical hysterectomy, a moderate exudate resulted postoperatively, very possibly due to a continued ooze retroperitoneally.

Pathological examination in all cases corroborated the gross findings noted clinically. No overt fistulous opening was demonstrated on section in the previously reported cases, but the local circulatory changes were clearly the result of an arteriovenous shunt. Microscopically, "irregular and variable vessel changes" were noted. Two authors stated that "differentiation between artery and vein was difficult." The mixed type of vessels described in our case suggested a combined artery and vein and might well be the anastomotic transition between the arterial and venous circulation.

The etiology of a uterine arteriovenous fistula must remain purely speculative at this time. The manifestation of this lesion so late in life would suggest an acquired factor; but evidence of trauma other than multiparity could not be found. A congenital origin is possible.

Follow-up examinations in the cases reported indicated that abdominal hysterectomy was sufficient to effect a cure and is therefore the therapy of choice.

Summary

An arteriovenous fistula within the uterus is a rare occurrence. Only three previous cases have been reported. A review of their distinctive features is presented.

The etiology of this unusual uterine vascular abnormality is undetermined.

The symptomatology and physical findings are sufficiently characteristic to suggest the diagnosis of this condition preoperatively. The usual presenting symptom is postmenopausal bleeding, sometimes of severe degree. The uterus is symmetrically enlarged and soft, simulating an intrauterine gravidity. A definite pulsation and thrill are palpable in the vaginal fornices. An audible murmur with systolic accentuation may be heard through the vagina. Systemic circulatory disturbances are minimal.

The pathologic findings of uterine arteriovenous fistulas are discussed.

At operation, numerous dilated, tortuous vessels fill the broad ligaments. The enlarged, distended, and vascular uterus may pulsate visibly. Surgical

eradication of the arteriovenous fistula is indicated. Diagnostic curettage may initiate formidable bleeding and is contraindicated. Abdominal hysterectomy with careful attention to hemostasis is the therapy of choice.

Addendum.—Since completion of this study, a somewhat similar case has been reported under the title of "Arteriectasia of the Uterine Artery."[10]

We wish to express our appreciation for the invaluable assistance given us by Dr. Sadao Otani in his painstaking investigation of the gross and microscopic pathology.

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A STUDY OF FETAL DISTRESS, ITS INTERPRETATION AND SIGNIFICANCE*

(From the Emanuel Hospital)

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THE prognostic importance of variations in fetal heart rate go back as early as 1833. Since then, fetal distress has been alluded to in many articles scattered throughout the obstetrical literature. However, despite the frequent reference to this condition, its interpretation, significance, and evaluation have never been satisfactorily investigated.

Obstetric texts[3, 4, 5, 6] have for many years stressed the importance of fetal heart auscultation. This importance increases as the first stage of labor nears its termination and the second stage is entered. Fetal heart auscultation thereafter is urged at very close intervals, stated as often as every five minutes or oftener if clinical factors deem it advisable.

The findings which are used most frequently to diagnose fetal distress pertain to changes in the behavior of the fetal heart.[3, 5, 12] These changes are specified as disturbances in rhythm, rate, or in the quality of the heart sounds themselves. A second sign leading to the diagnosis of fetal distress has been the passage of meconium[5, 8, 12] in other than sacral presentations. A third criterion has been an increase in fetal activity.[3, 12]

There are approximately four obstetric conditions wherein the development of fetal distress should reasonably be anticipated. These are the abruption of the placenta, placenta previa, prolapsed cord, and tumultuous labor and descent. All four alter fetal physiology in a detrimental or even fatal manner as is well recognized. When confronted with the probable or certain diagnosis of one of these four conditions, every obstetrician should be instantly aware that the fetus is in jeopardy.

It is not within the scope of this paper to set forth the diagnostic findings present in these conditions.

The occurrence of a palpable or visible prolapsed cord has set agile minds to work envisioning an "occult" or a trapped cord in the lower uterine segment. As the cord is literally the "life line" of the fetus, other worrisome placements or conditions have become legendary in producing fetal distress. These are loops of cord around the neck, under the arm, between the legs, or around a foot; a knot in the cord; a rupture of a marginal sinus; or a pathologically short cord.

With the exception of occult cord entanglement, all these conditions can be strongly suspected or diagnosed with certainty from the clinical picture.

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It is with the exclusion of these clinically recognizable entities that we interpret the allusion to fetal distress in the literature.

The entity of fetal distress with no demonstrable cause is an intriguing diagnosis and as interpreted above was the reason for this investigation.

A review of the recent literature disclosed that American investigators have given little time to this subject in the past few years and not much has been added since the basic observations of the founders of obstetrics in this country. Foreign investigators have been more active in attempting to analyze the fetal heart tones as a criterion of fetal distress.

The types of rates and/or rhythms commonly taken to indicate fetal distress are as follows: (1) rapid rate, over 160; (2) slow rate, under 100; (3) fluctuating rate; and (4) irregular rate.

The predominant opinions concerning these types of rhythm disturbances have been reviewed by Abraham and Dyer[2] in 1949. They are set forth below.

1. Rapid Rate.—King[10] believes that rates up to 170 to 180 are an infallible sign of fetal distress; Richardson[15] feels that such increase in rate may be the earliest evidence of abruptio placentae.

2. Slow Rate.—This is given more grave significance than rapid rate, especially when persistent, and may indicate true knot in the cord, coil around the neck with tension, or a prolapse of the cord.

3. Fluctuating Rate.—From slow to fast or vice versa. The importance of this finding is stressed in the foreign literature especially. It is believed to be associated with marked vagal stimulation and accompanied by efforts to breathe.

4. Irregular Rate.—This is not significant during a contraction according to King but serious when present between contractions.

Recently, however, articles have appeared in the foreign literature which seriously question the validity of these observations. One article[20] which appeared in the *Zentralblatt fur Gynäkologie* (Leipzig) by Thiele and Braun of the Giessen University Woman's Clinic offers statistics which show that the fetal heart tones are a very vague and inaccurate means of diagnosing fetal distress and have practically no value in establishing a prognosis for the fetus. The authors show that in a series of 89 cases, two-thirds of the newborn who had shown fetal distress of various nature cried immediately at birth and presented no sign of embarrassment.

The conclusions drawn by these German authors from their statistics are as follows:

1. The common belief that fetal heart tone disturbances have more significance during the second stage than during the first stage is not substantiated statistically.
2. Slow heart tones during the second stage are not a more serious sign than other types of rate anomalies.
3. One is not justified in attempting to make a prognosis about the fetus from the behavior of the fetal heart tones.
4. There is no correlation between the duration of the fetal distress and the amount of asphyxia shown by the infants at birth, which casts some doubt on the advisability of hurried and sometimes traumatic intervention to deliver the infant on the basis of fetal heart tone findings.
5. Premature infants do not appear to be more prone to fetal heart tone disturbances than mature fetuses.
6. Fetal heart tone disturbances are just as frequent in cephalic as in breech presentations.

In another paper[13] from the Spanish-speaking countries, Mercado states that he "no longer believes what the authors state about fetal heart tones." He relates some of his cases where infants who had been given up for dead on the basis of absent fetal heart tones, made a noisy entry into the world, causing some commotion among their parents and relatives who had resigned themselves to a stillbirth.

Many cases have been reported of infants being born in excellent condition after many hours of fetal heart disturbances. In some of these cases a section which had been thought indicated in the interest of the fetus was not done for various reasons.

As the above-mentioned German authors conclude in their study, "a revision of the ideas which have been handed down to us on the significance of the fetal heart tones and their interpretation in case management appears in order at this time."

In another recent study,[1] Abolins of the Pro Patria lying-in hospital in Stockholm reviewed 10,000 deliveries during the years 1940 to 1950. There were 115 cases of slow fetal heart tones, 22 cases of rapid fetal heart tones, and 36 cases of irregular heart tones. There were 23 cases of deep asphyxia or stillbirth in which there had been no change in the fetal heart rhythm. The statistics are quite similar to those from the Giessen Clinic previously mentioned. In Abolins' conclusion, he wishes to introduce a new class of fetal heart tones showing qualitative changes which are deemed more significant prognostically than the classification of rhythm disturbances. The fetal heart tones fall into this new class when they change from a strong to a weak "monotone-embryonal" type of beat.

It is hoped that current[11] and future observations of fetal heart physiology as gleaned from antepartum and intrapartum fetal cardiography will shed valuable light on this unexplored phase of fetal physiology.

The incidence of fetal distress varies considerably; most statistical surveys are available only from the foreign clinics. The Giessen Clinic had an incidence of 5.9 per cent; Zurich, 6.5 per cent; Koenigsberg, 13.6 per cent; Wuertzburg, 22.8 per cent; Stockholm, 3 per cent.

The importance of obtaining an infant in a healthy, robust condition makes the approach to this subject a difficult one. Unfortunately our coding system does not permit reviewing those cases in which a cesarean section was abandoned for some reason and the baby born in good condition. All cases that presented the above-mentioned criteria of distress were not so labeled because some of our staff do not place such importance on them. In reviewing the stillbirths and neonatal deaths, if any had shown distress and were not coded, they were included in our series.

Actually, the only criterion that we are left with as valid evidence of fetal distress is the immediate postnatal condition of the baby. This in itself may be misleading because we have no way of accurately assessing the baby's condition if nothing has been done in the presence of fetal distress, i.e., if there has been no hasty accouchement forcé.

On this premise, we have graded the amount of resuscitation each baby required in the cases diagnosed as having fetal distress prior to delivery. The amount of resuscitation is classified as follows: 0, none needed; 1+, oxygen and mild physical stimulation; 2+, oxygen with artificial respiration and occasionally tracheal catheter; 3+, oxygen and warm tube bath immersion; 4+,

oxygen plus drugs for respiratory and/or cardiac stimulation. The changes in fetal heart rate and rhythm were classified exactly as previously stated, namely: rapid (over 160 per minute); slow (under 100 per minute); fluctuating (from rapid to slow and slow to rapid); irregular (no specific rate). This has been enlarged in our series to include the combinations of irregular rhythm with the rapid, fluctuating, and slow rate. All these classifications deal with the predominant change or variations observed. The appearance of meconium in all but sacral presentations was also tabulated. Increased fetal activity as a criterion for fetal distress was not encountered in the charts reviewed.

Our series of fetal distress embraces 173 cases diagnosed during the years 1950-1951. During this period there were 8,785 deliveries, giving an incidence of 1.97 per cent.

Table I shows these cases tabulated as to division between primiparous and multiparous patients, amount of resuscitation needed, and the fetal outcome. The code letters refer to case-history summaries which are to be found at the end of the paper. It will be noted that 7 of the 10 infants who died postnatally required more than minimal supportive help in maintaining vital functions. However, it is worth while noting that these same 7 are in a group of 23 requiring 2+, 3+, and 4+ resuscitation. The other 16 survived. The total fetal loss in the series is 14, or 8 per cent.

TABLE I. TOTAL NUMBER OF CASES OF FETAL DISTRESS

	RESUSCITATION NEEDED					STILL-BORN	NEONATAL DEATHS
	None	1+	2+	3+	4+		
Primiparas 72	P	EG			R	BCD	EGPR
	43	18	3	2	3	3	4
			K	F	HLMN	A	FHKLMN
Multiparas 101	65	20	6	3	6	1	6
Total 173	108	38	9	5	9	4	10

Letters refer to case summaries.

Table II, similarly set up, lists those infants showing only fetal heart disturbances. It is thus shown that the same 7 infants mentioned above remain in this group. They are now included in a group of 14 requiring 2+, 3+ and 4+ resuscitation.

TABLE II. NUMBER OF CASES OF FETAL DISTRESS BASED ON FETAL HEART TONE FINDINGS ALONE

	RESUSCITATION NEEDED					STILL-BORN	NEONATAL DEATHS
	None	1+	2+	3+	4+		
	P	E			R	BCD	EPR
Primiparas 53	35	11	0	2	2	3	3
			K	F	HLMN	A	FHKLMN
Multiparas 77	51	15	4	2	4	1	6
Total 130	86	26	4	4	6	4	9

Letters refer to case summaries.

TABLE III. NUMBER OF CASES OF FETAL DISTRESS DIAGNOSED FROM EXCESSIVE MECONIUM ALONE (CEPHALIC PRESENTATIONS)

	RESUSCITATION NEEDED					STILLBORN	NEONATAL DEATHS
	None	1+	2+	3+	4+		
Primiparas 7	1	4	2	0	0	0	0
Multiparas 10	5	2	0	1	2	0	0
Total 17	6	6	2	1	2	0	0

Table III depicts fetal distress based on the passage of meconium in cephalic presentations. The group is small but it would appear that this as a solitary criterion of distress is not borne out by the fetal outcome.

Table IV shows the cases of fetal distress in which fetal heart disturbance plus the presence of meconium was used as a criterion. Here again the group is small with only one fetal loss. This infant required no resuscitation to speak of. Therefore, this combination of factors seems to have no significance for prognosticating fetal outcome.

TABLE IV. NUMBER OF CASES OF FETAL DISTRESS DIAGNOSED FROM MECONIUM PLUS FETAL HEART TONE CHANGES

	RESUSCITATION NEEDED					STILL-BORN	NEONATAL DEATHS
	None	1+	2+	3+	4+		
		G					G
Primiparas 12	7	3	1	0	1	0	1
Multiparas 14	9	3	2	0	0	0	0
Total 26	16	6	3	0	1	0	1

Letters refer to case summaries.

Table V shows the relationship between the type of fetal heart disturbance present with the resuscitation required. It will be noted that the heart rates slow, slow and irregular, and irregular comprise 79 per cent of all the types of fetal heart disturbance. The fetal loss in this group is 8.8 per cent. If computed for the individual rates, we see that the percentage fetal loss is 10 per cent, 0 per cent, 8.2 per cent, 0 per cent, 25 per cent, 0 per cent, and 20 per cent, respectively.

TABLE V. TYPE OF FETAL HEART TONE DISTURBANCE

	NO. OF CASES	RESUSCITATION NEEDED					STILL-BORN	NEO-NATAL DEATHS
		NONE	1+	2+	3+	4+		
Rapid	10	8	1	0	0	1	0	1
Rapid and irregular	6	4	1	1	0	0	0	0
Slow	73	44	16	3	4	4	2	4
Slow and irregular	25	18	5	2	0	0	0	0
Fluctuating	8	4	3	1	0	0	0	2
Fluctuating and irregular	9	8	1	0	0	0	0	0
Irregular	25	16	5	0	0	2	2	3
Total	156	102	32	7	4	7	4	10

The preceding five tables include all cases of fetal distress. Table VI sets forth just the cases of fetal distress in which no clinically demonstrable cause was present. Our corrected incidence of fetal distress therefore is 1.56 per cent (137 cases). It is noted that there were 2 stillbirths and 4 neonatal deaths. Three of the latter required 4+ resuscitation. The fetal loss in this

TABLE VI. CASES OF FETAL DISTRESS EXCLUDING ABRUPTIO PLACENTAE, PLACENTA PREVIA, AND PROLAPSED CORD

		RESUSCITATION NEEDED					STILL-BORN	NEO-NATAL DEATHS
		NONE	1+	2+	3+	4+		
			G			R	C	GR
Primiparas	61	38	15	3	2	2	1	2
						HM	A	HM
Multiparas	76	50	16	5	0	4	1	2
Total	137	88	31	8	2	6	2	4

Letters refer to case summaries.

group was 6, or 4.3 per cent. Our uncorrected fetal mortality for the 8,785 deliveries for this period (1950-1951) was 2.43 per cent.

Table VII compares the cephalic presentation fetal distress cases to the breech cases. It will be seen here as well as in Table I that there were 7 fetal deaths among the primiparas and 7 among the multiparas. However, although these fetal deaths are almost evenly distributed among primiparas and multiparas within each category of cephalic and breech cases, the incidence of fetal loss is more than six times greater in the latter. The fetal death rates, respectively, are 5.7 per cent and 35.7 per cent.

Six of the deaths in these two groups occurred with the finding of slow fetal heart tones. Five deaths were associated with irregular rates.

Fetal distress was diagnosed twice as often in the second stage of labor in the cephalic presentations and was about equally distributed between the first and second stages in breech presentations. There were only a few cases noted before labor.

Significant resuscitation for cephalic presentation was required in 21 cases, and in 3 cases for breech presentation. The ratio is almost twice as high for the cephalic cases which is paradoxical considering the higher breech fetal death rate. It will be noted too that 3 of the 4 stillbirths for the entire series were in the cephalic group. Theoretically, therefore, we should expect more neonatal deaths in the cephalic group if we are to use the degree of asphyxia requiring resuscitation as an index of the degree of fetal distress thought to

TABLE VII. COMPARISON OF FETAL DISTRESS IN CEPHALIC AND BREECH PRESENTATIONS

		CEPHALIC PRESENTATION 159 CASES			BREECH PRESENTATION 14 CASES		
		PRIMIP.	MULTIP.	TOTAL	PRIMIP.	MULTIP.	TOTAL
Signs of Fetal Distress.—	Rapid	2	3	5	0	1	1
	Rapid and irregular	1	2	3	1	0	1
		R	AM		C	FN	
	Slow	19	39	58	1	4	5
					E		
	Slow and irregular	5	14	19	2	1	3
	Fluctuating	P					
	Fluctuating and irregular	5	2	7	0	0	0
		4	2	6	1	0	1
		BD	HK			L	
	Irregular	10	8	18	1	2	3
	Meconium	7	10	17	0	0	0
		G					
	Meconium and FHT changes	12	14	26	0	0	0
When Fetal Distress Occurred.—	Before labor	2	5	7	1	1	2
	First stage	24	26	50	3	2	5
	Second stage	41	67	108*	2	5	7
Type Delivery.—	Cesarean section	18	21	39	5	1	6
	Vaginal delivery	47	73	120	1	7	8
Resuscitation Needed.—	None	38	62	100	4	4	8
	1+	17	19	36	1	1	2
	2+	3	6	9	0	0	0
	3+	2	2	4	0	1	1
	4+	4	4	8	0	2	2
		BD	A		C		
Fetal Outcome.—	Stillborn	2	1	3	1	0	1
		GPR	HKM		E	FLN	
	Neonatal death	3	3	6	1	3	4

*Six cases with distress present in first and second stages.
Letters refer to case summaries.

TABLE VIII. CESAREAN SECTIONS PERFORMED FOR FETAL DISTRESS

		OTHER INDICATION PLUS FETAL DISTRESS							
		FETAL DISTRESS ALONE	ABRUPTIO PLACENTAE	PLACENTA PREVIA	CEPHALO-PELVIC DISPROPORTION	MALPRESENTATION	PROLAPSE OF CORD	TOXEMIA	TOTAL
Signs of Fetal Distress.—	TOTAL	17	12	4	6	3	2	1	45
	Rapid	0	2	0	1	0	0	0	3
	Rapid and irregular	2	0	1	1	0	0	0	4
	Slow	4	4 E	0	0	1	0	0	9
	Slow and irregular	3	3 P	0	0	1	1	0	8
	Fluctuating	1	1	0	0	0	0	1	3
	Fluctuating and irregular	3	0	0	2	0	1	0	6
	Irregular	4 R	2	2 KL	2	0	0	0	10
	Meconium	0	0	1	0	1	0	0	2
	Meconium plus FHT changes	6	0	0	0	1	0	0	7
Resuscitation Needed.—	None	14	7 P	1	5	2	1	1	31
	1+	1	5 E	0	1	1	0	0	8
	2+	1	0	1 K	0	0	1	0	3
	3+	0	0	0	0	0	0	0	0
	4+	1 R	0	2 L	0	0	0	0	3
Neonatal Deaths.—		1 R	2 EP	2 KL	0	0	0	0	5
Stillborn.—		0	0	0	0	0	0	0	0

Letters refer to case summaries.

be present during labor. However, the breech series is too small to permit this conclusion.

Table VIII lists the 45 cesarean sections performed in this series of 173. As is shown, 17 cases were performed solely for fetal distress with no demonstrable pathology to account for the fetal disturbance. It will be noted that only one infant succumbed in these 17 cases. That infant had multiple congenital anomalies which were incompatible with neonatal life.

The other 4 neonatal deaths were associated with two conditions previously cited as jeopardizing the fetus' vital physiologic processes, namely, abruptio placentae and placenta previa. There were no stillbirths in this group. As previously pointed out, the preponderance of cases (27 in this group of 45) presented slow, slow and irregular, and irregular fetal heart disturbances.

If our premise of distress related to resuscitation required is valid, the question is raised as to the necessity of any of these 17 sections.

Table IX shows all cases of abruptio placentae, placenta previa, and prolapsed cord during the two years under study. The figures point out those cases presenting distress and those which did not. The highest ratio was in

TABLE IX. ALL CASES OF ABRUPTIO PLACENTAE, PLACENTA PREVIA AND PROLAPSED CORD

		ABRUPTIO 164 CASES			PLACENTA PREVIA 45 CASES			PROLAPSED CORD 20 CASES		
		PRIMIP.	MULTIP.	TOTAL	PRIMIP.	MULTIP.	TOTAL	PRIMIP.	MULTIP.	TOTAL
Fetal distress absent		33	104	137	13	29	42	4	10	14
Fetal distress present		7	20	27	0	3	3	4	2	6
Signs of Fetal Distress.—	Rapid FHT	0	2	2	0	0	0	0	0	0
	Rapid and irregular	0	0	0	0	0	0	0	0 FN	0
	Slow	3 E	11	14	0	0	0	0	2	0
	Slow and irregular	1 P	4	5	0	0	0	0	0	0
	Fluctuating	1	0	1	0	0	0	0	0	0
	Fluctuating and irregular	0	1	1	0	0 KL	0	0 BD	0	0
	Irregular	0	1	1	0	2	2	4	0	4
	Meconium alone	1	1	2	0	1	1	0	0	0
	Meconium with FHT changes	1	0	1	0	0	0	0	0	0
When Fetal Distress Occurred.—	Before labor	1	2	3	0	1	1	1	0	1
	First stage	1	9	10	0	1	1	1	0	1
	Second stage	5	9	14	0	1	1	2	2	4
Type of Delivery.—	Cesarean section	2	11	13	7	23	30	1	1	2
	Vaginal delivery	38	113	151	6	9	15	7	11	18
Resuscitation Needed Excluding Distress Cases.—	None	20	72	92	8	15	23	0	4	4
	1+	5	15	20	3	9	12	1	0	1
	2+	0	1	1	2	2	4	0	0	0
	3+	2	1	3	0	2	2	0	2	2
	4+	2	2	4	0	0	0	1	0	1
Neonatal Deaths Excluding Distress Cases.—	Mature	0	3	3	0	0	0	0	1	1
	Premature	5	11	16	1	3	4	1	2	3
Stillbirths Excluding Distress Cases.—	Mature	1	4	5	0	0	0	0	0	0
	Premature	3	9	12	0	2	2*	2	4	6
True prolapse		–	–	–	–	–	–	6	10	16
Occult prolapse		–	–	–	–	–	–	2	2	4

*One was second twin.
Letters refer to case summaries.

the cases of prolapsed cord (1:2); abruptio placentae was next with a ratio of 1:5, and placenta previa with 1:14.

This is in accord with the suddenness and/or severity with which the fetus is separated from the maternal lifeline.

It should be noted here that the 4 cases of occult prolapse of the cord showed no distress, all delivered vaginally, and there were no deaths.

Resuscitation for the distress cases is included in our other tables and we thought it interesting to compare the amount of resuscitation required for those infants not showing distress. We see that 2+, 3+ or 4+ resuscitation was required in 17 cases. These 17 are found in a total of 193 cases. Referring back to Table VI, there were 16 requiring similar resuscitation out of 137 cases. The respective ratios are 1:11.3 and 1:8.5.

The over-all fetal loss in those cases not showing distress (193) was 52, or 26.8 per cent. The mortality in this same group showing distress (36) was

8, or 22.2 per cent. It would certainly seem more reasonable to find the mortality higher instead of lower in the babies showing distress if the criteria for fetal disturbance have any validity.

Table X tabulates the 214 cases of fetal loss for the two-year period, 1950-1951.

Only 4 of the 90 stillborn babies showed distress. This is reasonably significant. Seventy mothers entered the hospital with absent fetal heart tones; the other 20 cases were intrapartum deaths. Sixteen infants succumbing before delivery and not showing some evidence of distress is a high figure, if we hope that fetal heart auscultation will be of prognostic value.

TABLE X. TOTAL FETAL LOSS (1950-1951)

		STILLBIRTHS 90 CASES	NEONATAL DEATHS 124 CASES	
		DISTRESS PRESENT	DISTRESS PRESENT	DISTRESS ABSENT
Signs of Fetal Distress.—	Rapid	0	0	–
	Rapid and irregular	0	0	–
		AC	FMNR	
	Slow	2	4	–
			E	
	Slow and irregular	0	1	–
			P	
	Fluctuating	0	1	–
	Fluctuating and irregular	0	0	–
		BD	HLK	
	Irregular	2	3	–
	Meconium	0	0	–
			G	
	Meconium and FHT changes	0	1	–
			EKLP	
When Distress Occurred.—	Before labor	0	4	–
		AB	FGHR	
	First stage	2	4	–
		CD	GHMN	
	Second stage	2	4	–
			DEKLP	
Type of Delivery.—	Cesarean section	0	5	–
		ABCD	FGHMN	
	Vaginal delivery	4	5	–
Resuscitation Needed.—	None		P	
		–	1	41
			EG	
	1+	–	2	36
			K	
	2+	–	1	6
			F	
	3+	–	1	10
			DHLMN	
	4+	–	5	21
		BA	EGHN	
Mature		2	4	30
		CD	DFKLMP	
Premature		2	6	84

Letters refer to case summaries.

There were 124 neonatal deaths in these two years, 10 infants showing fetal distress. The remaining 114 fetal deaths in the postnatal period are tabulated as to resuscitation needed. Thus 35 required 2+, 3+, and 4+ resusci-

tation. Instead of drawing conclusions from the infants requiring a considerable amount of resuscitation, it is more significant to note the large number requiring minimal stimulation who regardless of the lack of depression subsequently died. We have purposely contradicted our tenets here because we feel that a critical analysis of the distressed infants that died must be the deciding factor.

CASE A.—(F-16239) This 28-year-old multipara was admitted in active labor at 40 weeks' gestation. She was taken to the delivery room with cervix completely dilated. After a saddle block was given with no drop in blood pressure, the fetal heart tones were reported slow, between 88 and 100. The patient was given oxygen. A 7 pound, 2½ ounce, stillborn female infant was delivered immediately by manual rotation and low forceps extraction. Death was attributed to cord entanglement. Autopsy was performed and did not reveal any abnormalities.

It is hard to conceive of doing more than was done in order to obtain a live baby. No explicit description of the position of the cord is recorded, or the rapidity of descent of the head.

CASE B.—(F-16865) This was a 25-year-old primipara admitted in early labor. The head was unengaged. She was given a knee-chest enema which was shortly followed by spontaneous rupture of the membranes. The fetal heart tones ceased to be heard when the cervix was almost fully dilated. A palpable cord was found. A seven pound, seven ounce, stillborn female infant was delivered by low forceps.

This case might clearly have been avoided if a knee-chest enema had not been given and if the danger of a prolapsed cord with an unengaged head had been given more consideration.

CASE C.—(F-12326) A 19-year-old primipara was admitted at 40 weeks' gestation in established labor. The patient was Rh negative and had mild pre-eclampsia. The infant was in breech presentation. Distress was diagnosed by slow fetal heart tones in the second stage. Breech decomposition (complicated by nuchal arm) and extraction were performed under nitrous oxide-ether-oxygen anesthesia. The infant, a male weighing 8 pounds, 15 ounces, was stillborn. Death was attributed to compression of the cord. Autopsy revealed erythroblastosis fetalis and marked patent ductus arteriosus.

This was clearly an unpreventable death from our fetal distress point of view.

CASE D.—(F-33311) A 41-year-old primipara was admitted in rapid and tumultuous labor at 34 weeks' gestation. The cervix was fully dilated in about 1½ hours. The presenting vertex had not descended into the true pelvis during the process of dilatation and the patient was prepared for sterile vaginal examination. At this time, the membranes ruptured spontaneously. The fetal heart tones became irregular. She was examined immediately and the right arm, vertex, and prolapsed cord were found to be presenting in the vagina. A stillborn male infant, whose birth weight was estimated between 3½ and 5½ pounds, was delivered immediately. Autopsy revealed the cause of death to be subarachnoid hemorrhage. There was aspiration of amniotic fluid.

This is the usual unfortunate outcome in a case of true prolapse of the cord. This death was felt to be avoidable if controlled rupture of the membranes had been performed a few minutes or more prior to their explosive rupture. However, this would have been before fetal distress had been diagnosed.

CASE E.—(F-32895) A 25-year-old primipara was admitted to the hospital at 33 weeks' gestation. She was a juvenile diabetic, difficult to control. She was, however, progressing uneventfully in her pregnancy until the present admission when she had a sudden splash of bleeding followed by rupture of the membranes. The heart tones were found to be slow and irregular. Abruptio placentae was diagnosed and an emergency cesarean section was done. The baby required 1+ resuscitation. His weight was five pounds, 5 ounces. The infant died 9 hours later. Autopsy was performed and revealed: (1) alveolar dysplasia; (2) hemorrhage in the left leptomeninges. Anesthesia was spinal.

This was a case of a premature infant showing signs of distress in the presence of a clinical abruptio placentae—a known baby-killer.

CASE F.—(F-19907) A 36-year-old multipara was admitted with a tumultuous clinical abruptio placentae at 30 weeks. The fetal heart tones were slow. She delivered spontaneously a living 1 pound, 14½ ounce, immature male by breech, who lived 75 minutes.

This was another irreversible circumstance leading to the infant's demise.

CASE G.—(F-19771) A 20-year-old primipara was admitted at 39 weeks' gestation in established labor with a brow (anterior) presentation. Progress of labor was satisfactory until the cervix was about 3 cm. dilated at which time the fetal heart tones became rapid, going up to 168 or 170. About an hour later the cervix was completely dilated and she was taken to the delivery room. The head was flexed manually and the occiput rotated to a right occipitoanterior. Low forceps were applied for extraction of the head with general anesthesia. The infant, who weighed 7 pounds, 7½ ounces, required 1+ resuscitation. The nurses' notes show that immediately prior to delivery there was passage of considerable thick, yellow meconium. The infant, at birth, presented a large liver and edematous face, and erythroblastosis was diagnosed. The hemoglobin was 40 per cent. A replacement transfusion was given. However, the baby's condition deteriorated and he died about 24 hours later. Autopsy was performed and confirmed the diagnosis of erythroblastosis fetalis. This case was interesting because the mother was a primipara and gave no history of having had a transfusion of Rh-positive blood in the past.

This case presented passage of meconium or possibly the typically yellow-gold amniotic fluid so often seen with an erythroblastotic infant was mistaken for meconium. At any rate the fetal heart rate did rise rapidly. It has been observed that fetal heart changes are occasionally encountered in pathologically diseased or maldeveloped infants.[6-10, 17]

CASE H.—(F-19008) A 41-year-old multipara was admitted in active labor at 40 weeks' gestation with a cephalic presentation. The cervix was a finger tip dilated. The blood pressure was 144/100. There was 1+ ankle edema and albumin 10 mg. per cent. The diagnosis of mild pre-eclampsia was made. On admission at 1:30 P.M. the fetal heart tones were distant and completely absent for one or two seconds at frequent intervals. The dilatation was then 1 cm. At 3:10 P.M. the cervix was 5 cm. dilated, station minus 2. The fetal heart tones were between 120 and 140, with occasional skipping of several beats. Oxygen was given at this point with no improvement. The patient was taken to delivery room and delivered under general anesthesia shortly thereafter. A male infant weighing 6 pounds, 10 ounces, was delivered and required 4+ resuscitation. He was born with three loops of cord around the neck and a tight knot. There were four attempts at respiration. The infant died 4 minutes later. Diagnosis shown by autopsy was aspiration pneumonitis and bilateral diffuse atelectasis.

This infant probably could have been saved by cesarean section. However, how many times are the same findings present with the baby delivered in good condition? We are sure the answer is many.

CASE K.—(F-18790) A 25-year-old multipara was admitted at 32 weeks' gestation for bleeding due to placenta previa. After admission there was a sudden episode of severe bleeding (300 c.c.) with a drop in blood pressure from 104/64 to 90/55. The fetal heart tones became irregular during this episode. Section was performed immediately under general anesthesia. The infant, a male weighing 4 pounds, 9 ounces, cried immediately. He died 7 hours later. Autopsy revealed the cause of death as "prematurity."

This is a case of fetal distress due to one of the known causes that alter fetal physiology. Despite this the baby required no resuscitation. Death followed, however.

CASE L.—(F-12250) A 34-year-old multipara was admitted at 28 weeks' gestation for bleeding due to placenta previa. The fetal heart tones were reported to be irregular. A cesarean section was done under general anesthesia. The baby (a male, weighing 2 pounds, 2½ ounces) required 4+ resuscitation. He died 2 hours after delivery. Autopsy was not performed. The suspected cause of death was prematurity.

This was a repetition of the situation of an immature infant who was unable to survive the rigors of placenta previa and premature entrance into the world.

CASE M.—(F-7661) A 26-year-old multipara was admitted to the hospital in active labor at 32 to 33 weeks' gestation with a cephalic presentation. Labor was precipitous. The fetal heart tones dropped to about 100 after a spinal anesthetic was administered. There was no drop in blood pressure. A male infant weighing 3 pounds, 12 ounces, was easily delivered with low forceps and required 4+ resuscitation. He lived 36 hours. Autopsy was performed and the diagnosis was atelectasis and prematurity.

It is hard to conceive of handling this case differently or expecting a more favorable outcome.

CASE N.—(F-644) A 26-year-old multipara was admitted at 42 weeks' gestation in established labor with a breech presentation (double footling). The membranes ruptured at 6 cm. dilatation and the fetal heart tones became slow (84 per minute). The patient was placed on the delivery table immediately and the cord was found to be prolapsed. The cervix was manually dilated and a female infant extracted under general anesthesia. Four plus resuscitation was given. The infant died shortly thereafter. The birth weight was 6 pounds, 14 ounces. Autopsy was performed and revealed asphyxia as the cause of death.

This infant might have been salvaged if the cord compression could have been relieved by holding the breech up long enough to prepare for a section. Possibly the manual dilatation of the cervix (advisability questioned) took too long. Prolapse and the resultant compression of the cord caused death in a very short space of time.

CASE P.—(F-27390) A 30-year-old primipara was admitted at 37 weeks' gestation following passage of blood. She also gave the history of a few irregular contractions. Fetal heart tones were found to be fluctuating between 60 and 160. Sterile vaginal examination was done and the diagnosis of abruptio placentae was made. Cesarean section was performed immediately under general anesthesia. The infant, a female weighing 4 pounds, 4 ounces, cried spontaneously at birth. She was placed in an incubator with continuous oxygen. Three days later slight icterus was noted and a systolic murmur was heard at the apex. Following this the baby's condition deteriorated and she died 18 days following delivery. The clinical diagnosis was cardiovascular anomaly. Autopsy revealed: (1) engorgement of both lungs; (2) bronchial secretions positive for *Streptococcus viridans*. The cause of death was terminal bronchial pneumonia.

This case represents more than an abruption as the cause of death, although this probably caused the change in the fetal heart rate. No asphyxia was encountered at birth. This death can hardly be attributed to either the fetal distress or the abruption.

CASE R.—(F-31491) A 35-year-old primipara was sectioned under general anesthesia after 7 to 8 hours in labor at 2.5 cm. cervical dilatation because the fetal heart tones slowed down to 60 and became irregular with pains. A premature 4 pound, 11 ounce, female infant was given 4+ resuscitation and was pronounced dead after taking a few breaths. The infant had multiple congenital anomalies—dwarfism, congenital absence of anus, clubfeet, congenital absence of vertebral bodies. Autopsy was not performed.

This case was briefly reviewed in the comments concerning Table VIII. The comment concerning Case G pertains here, as well as for Case C, relative to diseased or maldeveloped fetuses.

In analyzing the 4 cases of stillborn infants who gave evidence of fetal distress, we feel that at the time of the occurrence of distress and the associated findings fetal disturbance was predictable in 2. The other 2 cases could not have been handled differently with the belated appearance of signs of fetal distress. One (Case C) would have had no other outcome regardless of management. Therefore, they should not be used to invalidate our conclusions.

Of the 10 cases of fetal distress which ended in neonatal death, we feel that only Case H might have had a more salutary outcome if more importance had been placed on the fetal heart disturbance early in labor. However, a

word of caution. Must we section 137 patients to salvage one infant with a condition which many many times is not lethal to the baby?

Analysis of the 6 deaths in the 137 cases (Table VI) allows us to correct our mortality rate from 4.3 per cent (6 cases) to 1.46 per cent (2 cases, A and H).

In the 137 cases, there were 2 deaths (Cases G and H) in which there were signs of disturbance in the first stage of labor and in which no recognizable reason for distress could be found. In the over-all series (173), distress occurred before labor and in the first stage in 64 cases. Subtracting those cases of abruptio placentae, placenta previa, and prolapsed cord in which distress was evidenced before labor and in the first stage (17), we are left with 47 cases. Seventeen of these patients were sectioned. Only one baby in this group died (Case R). This case is reviewed elsewhere. In the other 16, no such convincing cord entaglement as was present in Case H was discovered. There were no deaths in the remaining 30 cases of vaginal delivery.

Summary

1. A survey is presented of 173 cases of fetal distress, encountered among 8,785 deliveries during the period 1950-1951, an incidence of 1.97 per cent.

2. Of these, 137 cases offered no clinical findings other than one or more signs commonly accepted as evidence of fetal distress, i.e., fetal heart changes, or meconium, or both. The corrected incidence is 1.56 per cent.

3. Analysis of these cases is presented in the accompanying text and tables.

Conclusions

1. Excluding those conditions which are known to jeopardize the survival of the fetus and which can be diagnosed from the clinical findings, fetal distress is a nebulous condition. Our figures show how unpredictable the infant's condition at birth will be. Infants that require major degrees of resuscitation often survive, and those requiring no support subsequently die.

2. This presentation is not a plea to discard fetal heart auscultation. That would be most foolhardy. Fetal disturbance is a very tangible condition, but only when it is preceded or accompanied by a recognizable clinical entity known to affect deleteriously the fetal organism.

3. Without the clinical picture of one of these entities, caution and deliberation are urged in the individual case management.[12]

We wish to thank the attending staff of Emanuel Hospital for allowing their cases to be reviewed; the house staff and nurses of Emanual Hospital for recording valuable information on the charts without which this paper would have been impossible; and A. R. W., A. E. S., and H. G. R. for translating foreign monographs.

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812 S. W. WASHINGTON STREET

THE RESULTS OF NISENTIL IN 1,000 OBSTETRICAL CASES

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(From the Margaret Hague Maternity Hospital)

FOR all physicians who practice obstetrics the first thought must be that the management of pregnancy and labor shall result in the delivery of a healthy baby and that the condition of the mother post partum shall be as nearly as possible unchanged from that prior to her pregnancy.

It is accepted by most that an analgesic agent used properly is a valuable adjunct in the management of labor. We are all aware of the many types and combinations of analgesics used in obstetrics, as well as of their dangers. We also know what constitutes a good analgesic from the standpoint of both mother and baby. No analgesic so far available is ideal from the standpoint of effectiveness and freedom from maternal and fetal distress.

With these thoughts in mind, and in an endeavor to find a more satisfactory analgesic agent, we used Nisentil Hydrochloride,* a recently synthesized analgesic of the piperidine group. Nisentil was first reported by Ziering and Lee[1] in 1947 and its chemical pattern is similar to that of Demerol.

Material

This paper presents the results obtained with Nisentil in 1,000 obstetrical patients delivered at the Margaret Hague Maternity Hospital, Jersey City, between Oct. 1, 1951, and July 31, 1952.

La Forge[2] in earlier work on Nisentil found that the best results were obtained when the drug was used in a dosage of 60 mg. In all but 14 of our cases the initial dosage was 60 mg.

Table I gives the dosage of Nisentil employed and also the combination of other medications used with Nisentil.

TABLE I. DOSAGE

40 mg.	5 cases
40 mg. and scopolamine, grain 1/150	7 cases
40 mg. and Seconal, grains 3	2 cases
60 mg.	154 cases
60 mg. and scopolamine, grain 1/150	782 cases
60 mg. and scopolamine, grain 1/150, and Seconal, grains 1½	1 case
60 mg. and scopolamine, grain 1/150, and Seconal, grains 3	9 cases
60 mg. and scopolamine, grain 1/150, and Alurate, grains 7	12 cases
60 mg. and scopolamine, grain 1/150, and Alurate, grains 3½	1 case
60 mg. and Seconal, grains 1½	4 cases
60 mg. and Seconal, grains 3	21 cases
60 mg. and Alurate, grains 7	2 cases

All injections were given subcutaneously and were repeated when necessary, with the closest interval 2 hours and the longest interval 8 hours. The first injection was given when labor was established and also when it was indicated by the patient's reaction. Our criterion for the establishment of labor is either when the uterine contractions are ten minutes apart or when cervical dilatation begins.

*Supplied by Hoffmann-La Roche, Inc., Nutley, N. J.

The time of administering the initial dose of Nisentil after labor started is shown in Fig. 1. This chart omits 64 cases which are not presented because of the varied combinations of medication.

One hundred eighteen patients received two doses and 8 patients received Nisentil three times during labor. The dosage used in repeating Nisentil varied. There were 16 cases in which 30 mg. was used, 62 cases in which 40 mg. was used, and 48 cases in which 60 mg. of Nisentil was the second dose. Of those patients who required a third injection of Nisentil, 3 were given 30 mg., 3 received 40 mg., and in 2 a 60 mg. dose was administered. Table II gives the hour intervals between repeated doses.

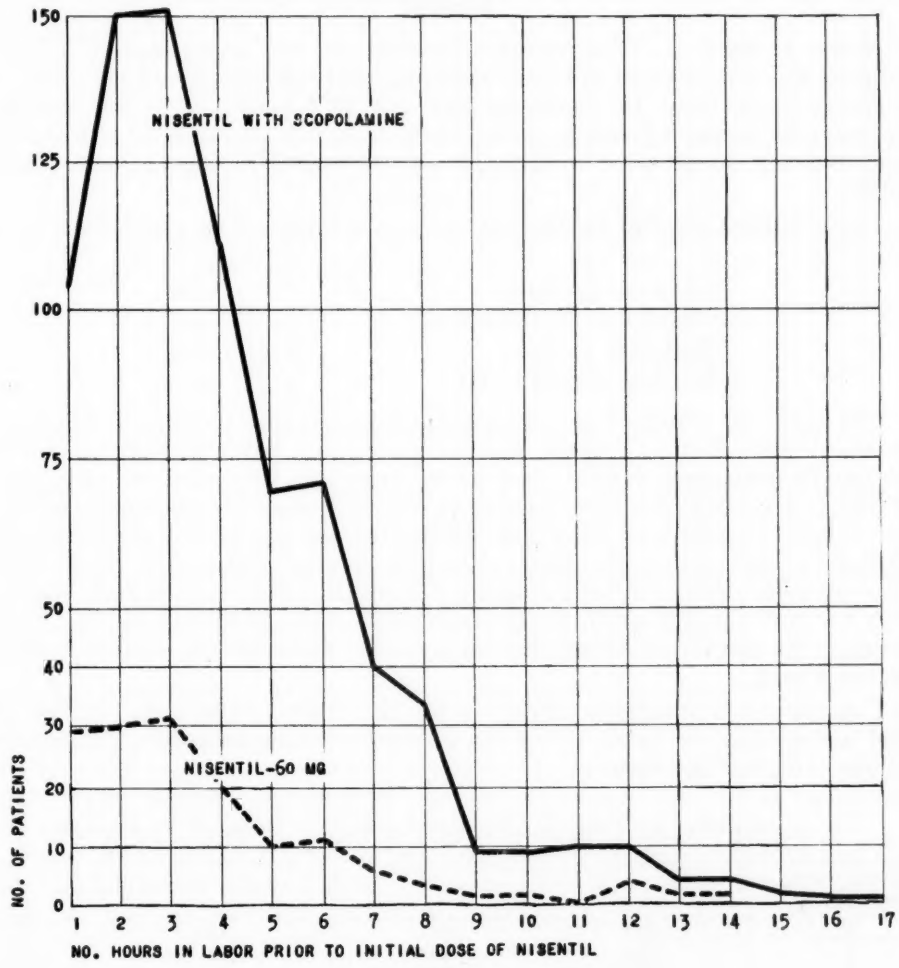

Fig. 1.

The anesthesia used for termination of the second stage was gas-oxygen-ether in 954 cases, spinal in 30, local in 10, open drop ether in 2, and no anesthesia in 4 cases.

There were only 2 cases in which labor was induced. There were 9 sets of twins. The presentation was vertex in 986, breech in 22, and transverse in 1, this being in a second twin. Nine hundred nineteen vertex deliveries were normal, spontaneous; there were 59 deliveries by low forceps, 7 by midforceps, 1 version and extraction, and 1 cesarean section for cephalopelvic disproportion. All the breech deliveries were normal, spontaneous.

TABLE II. TIME INTERVAL BETWEEN REPEATED DOSES OF NISENTIL

HOURS BETWEEN REPEATED DOSES	MILLIGRAMS OF NISENTIL					
	SECOND DOSE			THIRD DOSE		
	30 MG.	40 MG.	60 MG.	30 MG.	40 MG.	60 MG.
2	3	9	4	2	–	1
3	3	13	12	–	2	–
4	5	20	13	1	1	1
5	1	13	8	–	–	–
Over 5	4	7	11	–	–	–

Results

Maternal Factors.—The youngest patient in this series was 16 years old, the oldest 45. There were 314 primigravidas and 686 multigravidas. The average duration of labor in primigravidas was 12.3 hours, with the average in multigravidas being 6.7 hours, both below accepted averages. La Forge[2] also stated that the duration of total labor was decreased in the patients receiving Nisentil.

The effect of Nisentil on the mother was symbolized in the following manner:

Little or no relief	0
Slight but definite relief	+
Moderate relief	++
Marked to full relief	+++

The only side effect of the drug noticed was that 8 patients remarked that they felt "very dizzy." There was no vomiting. Nisentil either alone or in combination with scopolamine and/or barbiturates produced an objective result within a matter of a few minutes and in 977 cases the maximum effect was noted within 15 minutes. Maximum effect did not necessarily indicate marked to full relief but rather the level of satisfactory analgesia that the individual patient reached with the initial dose of Nisentil. Maximum effect was noted within 5 minutes in 101 cases, 10 minutes in 614 cases, 15 minutes in 262 cases, 20 minutes in 21 cases, and 30 minutes in 2 cases. The onset of maximum effect is shown in Fig. 2.

The combined analgesic effect of all the initial injections of Nisentil is shown graphically in Table III. The 0 number of hours refers to the time of maximum effect of the drug.

TABLE III. COMBINED EFFECT OF ALL THE INITIAL NISENTIL INJECTIONS

HOURS AFTER INJECTION	+++	++	+	0
0	844	141	12	3
1	806	168	21	5
2	433	253	54	4
3	135	273	81	7
4	29	137	137	11
5	2	28	57	6

The effect of Nisentil (60 mg.) is shown in Table IV, Nisentil (60 mg.) with scopolamine (grain $\frac{1}{150}$) in Table V, Nisentil, barbiturates, and/or scopolamine in Table VI.

Where Nisentil was used alone, the duration of maximum effect was between two and three hours. Where Nisentil was used with scopolamine (grain $\frac{1}{150}$),

TABLE IV. EFFECT OF NISENTIL, 60 MG.

HOURS AFTER INJECTION	+++	++	+	0
0	101	48	5	–
1	90	53	11	–
2	35	41	23	2
3	7	33	19	3
4	–	8	16	1
5	–	–	2	2

TABLE V. EFFECT OF NISENTIL, 60 MG., WITH SCOPOLAMINE, GRAIN 1/150

HOURS AFTER INJECTION	+++	++	+	0
0	681	91	7	3
1	655	112	10	5
2	360	200	31	2
3	114	222	59	4
4	19	94	117	6
5	2	28	55	4

TABLE VI. EFFECT OF NISENTIL WITH BARBITURATES AND/OR SCOPOLAMINE, GRAIN 1/150

HOURS AFTER INJECTION	+++	++	+	0
0	58	1		
1	58	1		
2	36	13		
3	14	18	1	
4	10	12	3	

the duration of maximum effect was about 1 hour longer than when it was used alone. Nisentil in combination with barbiturates and/or scopolamine had a more prolonged effect.

The response to repeated doses was excellent, with 107 of the 134, or 80 per cent, obtaining full or marked relief at a maximum level. The duration of this level for repeated doses was in proportion to the amount used.

The results were reported as satisfactory in 98.1 per cent of all cases. This report was made after labor had been completed and was an evaluation by both patient and delivery floor staff. Results were unsatisfactory in 1.9 per cent of all cases as far as analgesia was concerned; 10 of these 19 patients also had an unsatisfactory response to other medication, including 1 to saddle block anesthesia. There were 4 patients in whom pain relief was reported as moderate but in the analysis by the staff their analgesia was termed unsatisfactory.

Fetal Factors.—The effect of Nisentil on the baby was determined by the degree of asphyxia immediately following delivery. Gas-oxygen-ether anesthesia was used in 95.4 per cent of all cases, and the degree of asphyxia may be attributed either to anesthesia or to Nisentil. There was no abnormality noted in the fetal heart beat following Nisentil medication.

Asphyxia was classified as slight, moderate, or marked. The total aphyxia present was 8.9 per cent, with 4.0 per cent being slight, 3.3 per cent moderate, and 1.6 per cent marked. Slight asphyxia was recorded if the baby did not cry immediately but did so after gentle tracheal suction or external stimulus. If the infant required mechanical aid to establish respiration the asphyxia was termed either moderate or marked, depending upon the degree. The E & J respirator and the Bloxsom air lock were the mechanical aids used. There seemed to be no relation between asphyxia and the time the drug was given prior to delivery.

TABLE VII. INTRAPARTUM AND NEONATAL DEATHS

CASE	TIME OF DEATH	GESTATION IN WEEKS	INFANT WEIGHT IN GRAMS	DELIVERY	NISENTIL (MG.)	TIME OF LAST DELIVERY DOSE BEFORE	ASPHYXIA COMMENT	
1	Intra-partum	41	5,200	NSD*	40	4 hours	—	Autopsy performed. No disease found.
2	Intra-partum	40	3,100	NSD	60	2 hours	—	Nisentil administered after disappearance of fetal heart beat.
3	Neonatal	25	680	NSD	40	5 hours	None	Premature and immature.
4	Neonatal	32	1,200	NSD	60	4 hours	None	Second of triplets, lived 20 hours.
5	Neonatal	32	1,210	NSD	60	4 hours	None	Third of triplets, lived 22 hours.
6	Neonatal	40	2,400	NSD	60	45 minutes	Marked	Hypertensive; thin, brown umbilical cord, maceration of hands and feet.
7	Neonatal	45	3,300	Midforceps	40	5 hours	Marked	Fetal distress. Delivered under spinal anesthesia. All others under gas-oxygen-ether.
8	Neonatal	35	2,470	Low forceps	60	2 hours	Moderate	Severe pre-eclampsia.
9	Neonatal	40	3,300	NSD	60	1 hour	None	Congenital heart disease.
10	Neonatal	41	3,640	Midforceps	60	5 hours	Marked	Tentorial tear found at autopsy.
11	Neonatal	40	3,230	NSD	60	3 hours	Marked	Tight loop of cord around the neck.
12	Neonatal	40	2,920	NSD	60	2 hours	None	Congenital heart disease.

*NSD, Normal spontaneous delivery.

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There were 5 antepartum fetal deaths, 2 intrapartum, and 10 neonatal deaths giving a fetal mortality rate of 1.7 per cent. There were no stillbirths nor neonatal deaths in the slightly asphyxiated group; there was 1 death in the moderately asphyxiated group, and 4 deaths in the markedly asphyxiated. Table VII lists the intrapartum and neonatal deaths.

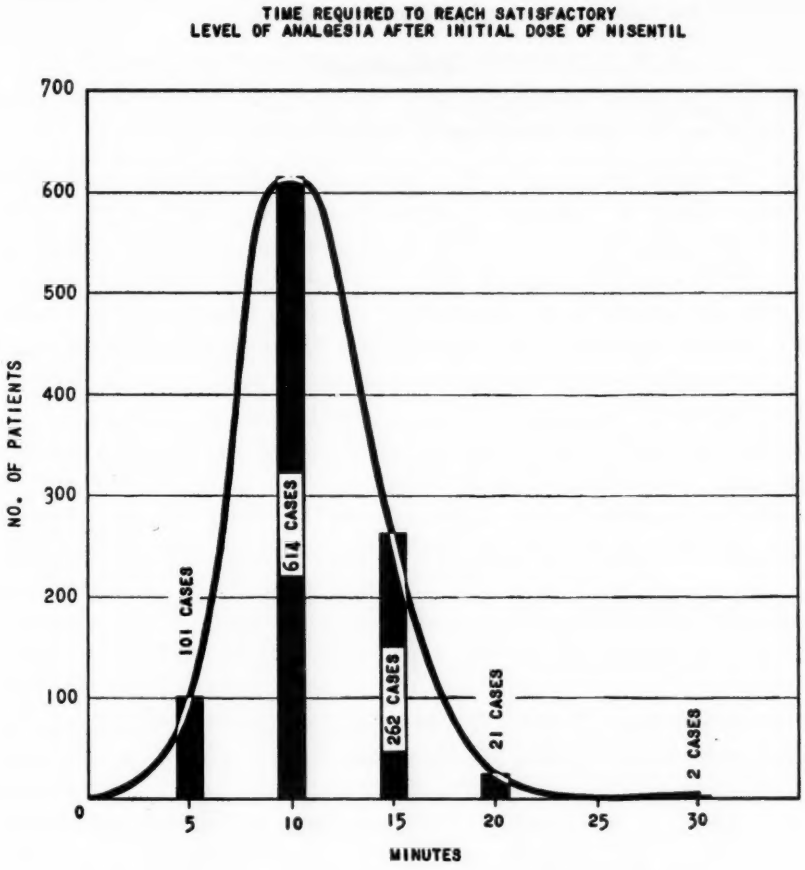

Fig. 2.

Conclusions

1. Nisentil Hydrochloride has been used in 1,000 obstetrical cases and found to give satisfactory analgesia in 98.1 per cent of the deliveries.

2. Nisentil (60 mg.) in combination with scopolamine (grain $\frac{1}{150}$) injected subcutaneously was found to give the best results. Nisentil may be repeated safely in proportion to subjective response.

3. There were no maternal side effects of Nisentil except in 8 patients (0.8 per cent) who complained of being very dizzy. There was no vomiting.

4. Fetal respiratory depression was present in either a moderate or marked degree in 4.9 per cent of the cases.

5. The over-all fetal mortality was 1.7 per cent. None of these deaths was attributable to Nisentil.

6. Nisentil is a valuable drug in obstetrical analgesia. Its rapid onset of action, relatively short period of maximum effect, and its minimal depression of respiration in the infant make it an almost ideal drug in the obstetrical field.

I wish to thank Drs. Samuel A. Cosgrove, Edward G. Waters, and John N. Connell for allowing the use of their clinical cases and the residents of the Margaret Hague Maternity Hospital for help in collecting the data.

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TRILENE,* AN ADJUNCT TO OBSTETRICAL ANESTHESIA AND ANALGESIA†

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SINCE Simpson administered the first obstetrical anesthetic in 1847 and von Steinbuchel gave the first obstetrical analgesic in 1902, obstetricians as well as their patients have fervently hoped for the panacea for obstetrical pain. It has not been found. But from the varied opinions which exist concerning obstetrical pain relief and the voluminous literature on the subject, it is quite evident that the majority of obstetricians have selected certain analgesic and anesthetic techniques that are at least individually satisfactory.

Some physicians hope to achieve complete analgesia, amnesia, and anesthesia. Others advocate natural childbirth and believe that parturition and labor should be physiological and practically painless. However, between these two extremes lie the majority of the American obstetricians who use various techniques of conduction anesthesia and who employ various dosage schedules of hypnotics, amnesics, and analgesics.

However, each new drug and analgesic technique that is introduced is met with curiosity and a hope that it will prove useful. It is thus that Trilene has been received in the United States.

Hewer[1] introduced trichlorethylene as both an analgesic and anesthetic agent. However, it is felt that in obstetrics the pharmacological action of the drug dictates its use purely as a potent analgesic, either alone or as an adjunct to other obstetrical anesthetic techniques.

Chemical Composition and Pharmacological Action

The clinical application of any drug is dependent upon its pharmacological action. Trilene has the following chemical formula $ClCH = CCl_2$. The color and smell of Trilene closely resemble those of chloroform. The boiling point is 86° C., making the vaporization of the drug insufficient for use on an open mask. It cannot be employed with soda lime, since toxic dichloracethylene is formed.

Table I[2] compares Trilene with chloroform, ethylene, and ether. It is apparent that Trilene is related to both chloroform and ethylene and shares some of the favorable characteristics of ethylene and a few of the unfavorable qualities of chloroform.

If one defines the margin of safety as a difference between the percentage of a given drug which will cause analgesia, and the percentage of the drug which will be fatal, it is evident that Trilene with at least a 3 per cent margin of safety is superior to chloroform which has a margin of 0.65 per cent but somewhat inferior to ether which has a safety margin greater than 8 per cent. Trilene's

*Purified trichlorethylene, Ayerst, McKenna and Harrison Limited, New York City.

†Presented at a meeting of the Brooklyn Gynecological Society, Nov. 19, 1952.

effect upon the respiratory and vasomotor centers is similar to that of ethylene and ether. Neither center is adversely affected whereas in chloroform both are depressed. Trilene depresses the vomiting center; thus the danger of aspiration of vomitus is negligible even in the unprepared obstetrical patient. This factor is of fundamental importance since one of the greatest dangers in obstetrical anesthesia is aspiration of vomitus.[3, 4]

The harmful effects of chloroform upon the liver have almost become legend.[5] Since the chemical formula of Trilene is closely related to that of chloroform, liver necrosis from Trilene was viewed as a possibility. However, Waters[6] and his colleagues have recently emphasized that in the presence of adequate glycogen, oxygen, protein, and skillfully administered anesthesia, chloroform produces negligible hepatic injury, possibly only slightly greater than ether. Armstrong[7] in his excellent monograph on "The Assessment of Liver Damage Following Trichlorethylene Anesthesia" asserts that the transient liver damage caused by trichlorethylene is less than that due to ether. Herzberg[8] has similarly shown that there is essentially no liver damage resulting from Trilene. However, if one wishes to maintain the maximum margin of safety it must be realized that ether and Trilene are both capable of producing slight glycogenolysis and only the well-hydrated patient should receive prolonged Trilene analgesia.

TABLE I. PHARMACOLOGICAL COMPARISON OF TRILENE*

	TRILENE $ClCH{=}CCl_2$	ETHYLENE $H_2C{=}CH_2$	CHLOROFORM $CHCl_3$	ETHER $H_5C_2{-}O{-}C_2H_5$
Analgesia	0.5%	25%	1.35%	Too irritating for use
Anesthesia	1.2%	85%	1.65%	4%
Respiratory arrest	Above 3.5%	Does not occur without anoxia	2.00%	Above 8%
Respiratory center	Stimulated	Not affected	Depressed	Stimulated
Vomiting center	Depressed	Not affected	Depressed	Stimulated in light anesthesia
Vasomotor center	Not affected	Not affected	Depressed	Not affected
Liver function	Function depressed less than with ether and chloroform	Not affected	Function depressed	Function depressed for 24 hours less than with chloroform—more than with Trilene
Heart	Unchanged in analgesia; fatal arrhythmias possible in deep anesthesia	Cardiac output and rhythm unchanged	Cardiac output decreased 30%; ventricular fibrillation possible	Cardiac output increased; minor Grade I arrhythmias
Lungs	Minute volume increased	Minute volume unchanged	Minute volume decreased	Minute volume increased
Explosion hazard	No	Yes	No	Yes

The effect of Trilene upon the cardiovascular system warrants serious consideration. All of the known anesthetic gases, ether, nitrous oxide, cyclopropane, chloroform, and Trilene may produce cardiac arrhythmias. These arrhythmias may be divided into two groups. Group I is due to increased vagal tone and is manifested by nodal rhythm, delayed auricular ventricular conduc-

tion, and bradycardia. They are generally not manifested clinically and they are considered harmless. Group II arrhythmias are dangerous and are manifested by multifocal ventricular tachycardia, cardiac standstill, and ventricular fibrillation. These may occur in moderately deep cyclopropane and light ethyl chloride and chloroform anesthesia. However, Group II arrhythmias occur only in the lower first and second plane of Trilene anesthesia.[9] Therefore, Trilene is recommended only for analgesia in obstetrics and with such use the danger of primary cardiac failure is negligible. Hingson has stated in reference to the previously reported[4] obstetrical deaths under Trilene, "None of these deaths were associated with Trilene as an analgesic, and were possibly caused by the use of impure trichlorethylene in the early development of the drug."[10] The pulmonary complications with Trilene analgesia are not important. The minute volume of inspired air is increased and tachypnea seldom occurs except when anesthetic concentrations of the drug are employed. Kidney function is unimpaired.

Method of Administration

In the hands of a well-trained anesthesiologist, Trilene may possibly be used for surgical anesthesia. But the place of Trilene in obstetrics is only for analgesia. It may be employed either alone or as an adjunct to other techniques of obstetrical pain relief. When Trilene is used purely for analgesia the pharyngeal reflexes are not abolished and aspiration of vomitus does not occur. Serious cardiac arrhythmias are avoided. In the presence of adequate glycogen, liver damage is unimportant. The index of safety is extremely high. Of great practical important is the fact that the agent may be self-administered with safety.

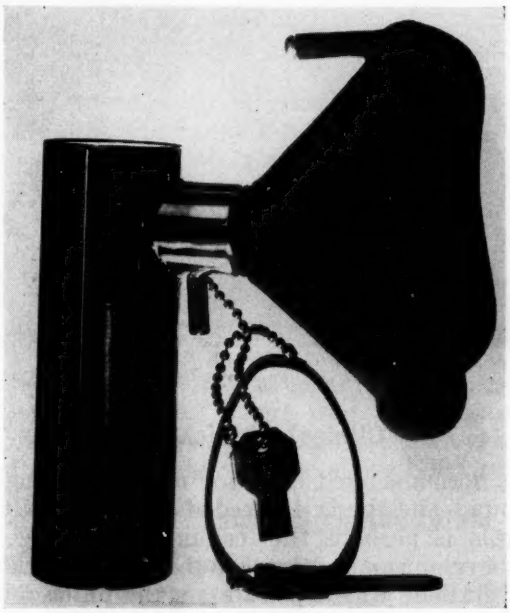

Fig. 1.

The success of Trilene administration depends directly upon the cooperation of the patient and the care that the obstetrician takes in instructing the patient in the use of the agent. The most practical and economical device for administering Trilene is the "Duke inhaler" designed by C. R. Stephen[11] (Fig. 1).

Fig. 2 represents the vapor concentrations at the various scale settings for the "Duke inhaler." It is evident that the maximum safety and usefulness of the drug in obstetrics are for analgesia. Thus, the scale settings on the inhaler should be at analgesic concentrations; this will vary between three and six inclusive. The vapor concentrations should be low until the patient is accustomed to the smell of Trilene; then the concentration should be raised until the desired depth of analgesia is achieved. The first two or three breaths of Trilene should be taken with the mouth open and the mask only loosely applied to the face. When Trilene is used in this manner there will usually be little objection to its smell.

The wrist strap should always be used during self-administration so that the inhaler may be allowed to fall from the patient's face when anesthesia approaches. When Trilene is administered to a patient with the inhaler the mask should always be removed when the patient loses consciousness. When these two safety factors are used, the patient will receive only analgesic concentrations of Trilene.

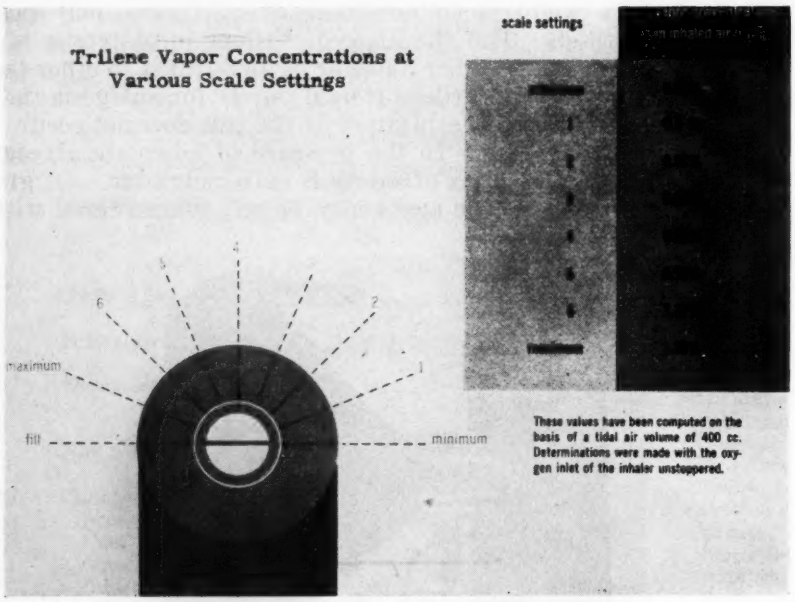

Fig. 2.

Clinical Application

Since Trilene is recommended only for obstetrical analgesia it should not be used when profound anesthesia is needed for a difficult delivery. In such cases spinal anesthesia is perhaps the technique of choice. When uterine relaxation is necessary cyclopropane-ether are the agents of choice.

The final use of Trilene will depend upon the philosophy of the individual obstetrician. For the obstetrical specialist who desires to have the patient unconscious under profound analgesia, Trilene will be useful only before the uterine contraction pattern has developed sufficiently to employ large doses of analgesic or hypnotic drugs.

For the general practitioner or the obstetrical specialist who advocates natural childbirth or minimal analgesia, Trilene is useful either alone or in combination with small doses of Demerol, Seconal, or Nembutal.

When pudendal block, spinal, caudal, or local anesthesia for cesarean section is not completely satisfactory, Trilene may be used as an adjunct.

For the average obstetrical specialist Trilene will find its greatest value as a general handy agent on the delivery floor. It is ideal for a precipitate delivery; it may be used successfully while the nurse is preparing analgesic drugs or the obstetrician is awaiting the arrival of the anesthesiologist. It is the safest analgesic agent for the infant when the patient arrives late in labor, and it is the safest agent available for the easy multiparous delivery.

It has been particularly valuable in the Kings County Hospital where the acute shortage of nurses and anesthetists previously made it impossible for all patients to receive analgesia and relief of pain at delivery.

Table II illustrates the use of Trilene in 602 patients. In 315 of these patients, Trilene was used either alone for analgesia in spontaneous delivery or in combination with small doses of Demerol and Nembutal. The five breech deliveries were for immature or premature infants presenting by the breech. Trilene was employed in combination with pudendal block with or without Demerol or Nembutal in 258 deliveries. There were 56 low forceps, 7 mid-forceps, and 5 operative breech extractions.

TABLE II. CLINICAL APPLICATIONS OF TRILENE

	NUMBER	SPONTANEOUS DELIVERY	FORCEPS	BREECH	FULL TERM	PREMATURE	IMMATURE
Trilene	315	310	0	5	290	20	5
Trilene pudendal block	258	190	63	5	247	11	0
Trilene spinal	15	0	15	0	15	0	0
Trilene caudal	10	0	10	0	10	0	0
Trilene local, cesarean section	4	–	–	–	4	0	0
Total	602	500	88	10	566	31	5

When Trilene was used as an adjunct to other types of analgesia for precipitate deliveries and for analgesia late in labor it was accepted by the patient with enthusiasm and almost universal satisfaction. When it was used alone or in combination with other analgesic drugs it was satisfactory in about 80 per cent of the cases. Ten per cent of the patients found the odor of Trilene objectionable and refused the inhaler. The majority of these patients were either uncooperative or presented a language barrier.

Table III shows that the incidence of postpartum hemorrhage and manual removal of the placenta was no greater than would be expected in uncomplicated vaginal deliveries. The incidence was less than the clinic average of 4 per cent.

There were 12 fetal deaths; 7 of the infants had no fetal heartbeat at the time of administration of Trilene. There were 4 deaths of immature infants and one death in a premature associated with several congenital anomalies. The corrected fetal loss of all infants who weighed above 1,000 grams was 0.

The Effect of Trilene Upon the Infant

There is no agent which will produce sedation or analgesia in the mother that does not traverse the placenta and become a potential cause of asphyxia neonatorum.[12, 13] The effect upon the infant will depend upon the concentration of the drug administered and the rapidity with which it is metabolized or eliminated. Trilene is no exception. But when it is administered as an analgesic agent to the mother, it will have only an analgesic effect upon the infant. Trilene is eliminated from the blood stream with the same rapidity as chloroform.[14] Thus, any depressant effect upon the infant will be transitory.

There were 6 infants in this series of 602 cases requiring positive pressure resuscitation. This is an incidence of 1 per cent which is the same figure reported by Gordon and Morton[15] in 669 obstetrical patients.

TABLE III. COMPLICATIONS WITH TRILENE

	OBSTETRICAL DIFFICULTIES					PERINATAL LOSS				
	TOTAL CASES	MATERNAL LOSS	MANUAL REMOVAL PLACENTA	POSTPARTUM HEMORRHAGE	POSITIVE PRESSURE RESUSCITATION	IMMATURES	CONGENITAL MALFORMATION	STILLBORN, FETAL HEART TONES ABSENT BEFORE ADM.	UNCORRECTED FETAL LOSS	CORRECTED FETAL LOSS ABOVE 1,000 GRAMS
Trilene alone	315	0	3	4	3	4	0	5	9	0
Trilene pudendal block	258	0	2	2	3	0	1	2	3	0
Trilene spinal	15	0	0	0	0	0	0	0	0	0
Trilene caudal	10	0	0	0	0	0	0	0	0	0
Trilene local, cesarean section	4	0	0	0	0	0	0	0	0	0
Total	602	0	5	6	6	4	1	7	12	0

TABLE IV. EFFECT OF TRILENE UPON THE INFANT

TYPE OF ANALGESIA	NO. OF INFANTS	PERCENTAGE OF INFANTS			NUMBER OF INFANTS		
		BREATHING TIME 1+ MIN.	CRYING TIME 2+ MIN.	POSITIVE PRESSURE RESUSCITATION	BREATHING TIME 1+ MIN.	CRYING TIME 2+ MIN.	POSITIVE PRESSURE RESUSCITATION
Trilene alone	50	4	2	0	2	1	0
Trilene with analgesic drugs	50	4	6	2	2	3	1
Control group, no anesthesia, no analgesia	140	3.5	5	2	5	7	3

Table IV represents a critical analysis of the effect of Trilene upon the infant. Breathing times and crying times were accurately obtained at 100 deliveries. The number of infants with breathing time in excess of 1 minute and crying time in excess of 2 minutes, and the number of infants requiring positive pressure resuscitation were essentially the same as in 140 randomly selected deliveries where no anesthesia or analgesia was administered.

This does not mean that Trilene will cause no depression to the infant. If Trilene is administered too long or in too great a concentration, it is possible to cause asphyxia neonatorum. It does signify, however, that the intelligent intermittent use of Trilene as an analgesic is not generally fraught with danger of fetal depression.

Summary

Trilene is a potent analgesic drug. Its margin of safety and ease of administration will ultimately make it a standard agent on all delivery floors. Trilene's wide variety of uses will probably allow almost every obstetrician to find a place for it in his obstetrical practice.

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DEFECTIVE BLOOD COAGULATION ASSOCIATED WITH PREMATURE SEPARATION OF THE PLACENTA

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ABNORMALITIES in the blood-clotting mechanism in toxemic patients were reported as long ago as 1887.[1] In 1901 DeLee[2] observed a hemorrhagic diathesis associated with a severe premature separation[3-6] of the placenta. Since then various observers have noted that blood specimens taken from patients with severe premature separation of the placenta will frequently clot slowly or not at all. Weiner and associates[7] noted a similar coagulation defect in patients in whom intrauterine death from Rh isosensitization occurred.

The etiology of the coagulation defect has not been definitely established. Several theories have been proposed to explain the mechanism of this disturbance. They are as follows:

1. Toxins affecting the liver. Weiner[7] suggests the presence of a toxic placental or fetal substance which depresses liver function. Consequently, fibrinogen which is normally produced in the liver is diminished in concentration in the plasma.

2. Intravenous clotting. Obata[8] reported that saline extracts of normal placenta injected into rabbits produced liver lesions characteristic of eclampsia as well as convulsions and coma. This was confirmed by Hayashi[9] using dogs. Schneider[10] stated that this substance was thromboplastin. He noted that the mere pinching of the pregnant rabbit uterus resulted in the release of so much thromboplastin from the placenta that intravascular clotting occurred. In 1951 he[11] suggested that retroplacental hematomas expanded to disrupt the enclosing basal plate with release from the hematoma of a mixture of blood and decidual debris into the maternal lake of the placenta. Since this is rich in thromboplastin, it produces a variable degree of intravascular clotting. This, in turn, produces a demonstrable lowering of the plasma fibrinogen, intravascular hemolysis, and a transitory increase in the icteric index.

3. Increased fibrinolysis. Tagnon and associates[12] define fibrinolysis as a complete dissolution of the fibrin clot produced by coagulation of whole blood or plasma in the time interval of a few hours. This is produced by a circulating fibrinolysin. They describe a case of postpartum hemorrhage treated with transfusion and hysterectomy. The patient died soon afterward. Whole blood taken shortly before death never clotted. After spinning, the supernatant fluid was added to a fibrinogen solution and it produced a clot which redissolved in one hour. Weiner and his group, however, were unable to demonstrate digestion of standard fibrin clots by the plasma of patients who showed coagulation defects associated with Rh isosensitization.

It has been shown that it is almost impossible to administer blood at a sufficient rate to raise the blood fibrinogen to effective coagulant levels. Each pint of blood with a normal fibrinogen level of 200 mg. per cent is so quickly diluted in the patient's circulation that effective fibrinogen increase is minimal. Fibrinogen itself must be given, and the effective dose must be at least 6,000 mg.

We recently had a case of severe premature separation of the placenta with profuse hemorrhage. Despite massive transfusions of bank blood and hysterectomy the patient died. In reviewing the case we felt that the hemorrhage was due to a defective clotting mechanism. Shortly afterward, a similar case was admitted and the management was directed at the correction of the coagulation defect. It is reported as follows:

Mrs. V. C., a 23-year-old Negro primigravida, was admitted to the hospital in the thirty-second week of gestation when routine prenatal check showed evidence of moderate pre-eclampsia. The only complaint was an occasional headache. Physical examination on admission revealed a temperature of 100.4° F., pulse 94, and a blood pressure of 170/110. Systemic review was normal except for a one-plus pretibial edema. On abdominal palpation the uterus was enlarged to eight months' size and the vertex presented in a left occipitoanterior position. On rectal examination the head was dipping and the cervix was uneffaced and closed. The fetal heartbeat was regular and of good quality.

Laboratory findings were reported as hemoglobin 12.5 Gm.; white blood cells 8,700; uric acid 8 mg. per cent; urea nitrogen 20 mg. per cent; and total protein 5.2 Gm. per cent with an albumin-globulin ratio of 1.1. Urinalysis showed 4-plus albumin and numerous red blood cells and white blood cells. Five days after admission 1 to 2 casts per high-power field were noted and an Addis count on a urine specimen with a specific gravity of 1.026 showed 60,000 casts, 7,500,000 red blood cells, and 1,500,000 white blood cells.

The patient was given sedation and placed on bedrest. For the first five days she ran a febrile course ranging as high as 102° F. During this time she had no subjective complaints. Chest x-ray revealed no pulmonary pathology. Antibiotic therapy was instituted empirically and the temperature gradually subsided. The blood pressure diminished but 4-plus albuminuria persisted. On the fifth hospital day the membranes ruptured spontaneously and meconium-stained amniotic fluid was passed. The fetal heartbeat, however, remained regular and of good quality. The vertex was found to be engaged at station O and the cervix was partly effaced and one finger tip dilated.

In view of the ruptured membranes and the toxemic status of the mother, an intravenous Pitocin induction was begun. Contractions followed immediately and the cervix was effaced and dilated progressively. After six hours of intravenous Pitocin the uterus suddenly became tense and the fetal heartbeat disappeared. No external bleeding was noted. On vaginal examination the cervix was found to be two fingers dilated and firm. Blood pressure and pulse were carefully followed but no evidence of concealed hemorrhage was detected. A presumptive diagnosis of premature separation of the placenta was made. Pitocin was continued for another three hours without any effect on dilatation or descent. The patient was then given heavy sedation, an infusion of 5 per cent glucose in water, and the Pitocin discontinued until the following morning.

It was noted now that the patient was markedly oliguric, having passed a total of 15 c.c. of dark red urine despite a 24 hour intake of 2,700 c.c. of fluid. Pitocin was restarted and in the following eight hours no appreciable progress was made. Oliguria persisted and the amniotic fluid was now foul-smelling. Accordingly, Dührssen's incisions were made under saddle-block anesthesia and a midforceps extraction of a stillborn male infant weighing 5 pounds, 2 ounces, was performed. On inspection of the uterus immediately post partum the placenta was found to be lying partially free. It was removed manually and found to have fresh infarctions. Bleeding did not appear to be excessive and the uterus remained well contracted. The cervix was repaired and the patient returned to the ward in fair condition.

During the next 12 hours the urinary output was 100 c.c. of clear amber fluid. Bleeding did not appear to exceed normal limits. Pulse and blood pressure were maintained and the uterus remained well contracted. The patient, however, appeared suddenly to grow worse. Pressure on the fundus expressed over 1,000 c.c. of semifluid blood. Shortly afterward, the patient went into profound shock. A cut-down was performed and bank blood given under pressure. Though the fundus appeared to be well contracted a continuous ooze persisted. The vagina and cervix were inspected and while there was no bleeding from the site of the Dührssen's incisions a diffuse ooze was noted from the lower genital tract. There were no bleeding points that could be ligated. The vagina was tightly packed. A total of 2,000 c.c. of citrated bank blood was given but the patient did not rally.

Two and one-half hours after the vagina was packed, bleeding through the packing was noted. It was felt that a defective clotting mechanism was present and a plasma fibrinogen level determination was ordered. In view of the urgency of the situation, 8,000 mg. of fibrinogen was administered rapidly without waiting for further laboratory data. The patient was taken to the operating room and the packing removed. It was noted that bleeding had almost completely stopped. Another 1,300 c.c. of bank blood was given and remarkable improvement in the patient's general condition was noted. The piasma fibrinogen level was later reported as 90 mg. per cent (normal 200 mg. per cent).

No unusual bleeding was noted thereafter. Urinary output increased and the patient showed progressively diminishing hypertension and albuminuria. She developed endometritis, however, and ran a septic course for two weeks. By the sixteenth postpartum day the temperature was normal. She was discharged after 27 days of hospitalization.

Comment and Conclusions

In the case we have reported there may have been several factors combining to produce the bleeding diathesis. There was an inadequate fibrinogen level as attested by the low level found in the blood specimen taken prior to transfusion with fibrinogen. In addition, the time lag between the delivery and the onset of active bleeding may be explained by possible fibrinolytic activity as described by Tagnon and co-workers.[12] Finally, Seegars[13] has described a substance called Ac-globulin found in association with the fibrinogen derivative of blood. It is essential for the rapid activation of prothrombin by calcium ions and thromboplastin. Johnson and collaborators[14] have shown that the Ac-globulin concentration of the maternal plasma in abruptio placentae drops to extremely low levels. It is possible that the critical level of Ac-globulin in the case reported was not passed until 12 hours post partum, but once the derangement occurred, evidence of the coagulation defect became rapid and dramatic. Whether one factor or a combination of factors was responsible for the postpartum hemorrhage, it is important to note that once the fibrinogen was given the patient stopped bleeding and thereafter showed no evidence of defective coagulation.

An explanation of why bank blood may be ineffectual in replacement therapy has been given by Seegars. He reports that the prothrombin level in blood remains normal for long periods of time but Ac-globulin disappears rapidly. In time it may be shown that still other essential substances in the blood are modified by storage. Mack and Dieckmann have demonstrated good

results with direct transfusion when citrated blood has proved inadequate. With fibrinogen extremely difficult to obtain, direct transfusion may be the therapeutic answer to some of the problems of blood derivative replacement.

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SPORADIC AND EPIDEMIC PUERPERAL BREAST INFECTIONS*

A Contrast in Morbid Anatomy and Clinical Signs

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CLINICIANS have long been aware that puerperal breast infections could be divided into those which occur sporadically and those which occur in epidemics, but I do not think it has generally been recognized that the division on epidemiological grounds also segregates the cases into two groups which are quite distinct in their morbid anatomy and in their clinical features. I shall compare and contrast the clinical signs in these two types of puerperal mastitis as they were seen before the introduction of chemotherapy, because it is only in this way that we can get a clear picture of the natural history of the diseases unmodified by treatment.

1. Acute Puerperal Mammary Cellulitis

The classical nonepidemic type of puerperal mastitis was a mammary cellulitis due to infection which had gained entrance through a cracked nipple. The clinical picture was typical. The mother would, perhaps, suffer from a cracked nipple on the third or fourth day of the puerperium; suckling would be discontinued (or perhaps allowed through a nipple shield) for 24 hours, and the crack would heal. A day or two later the fissure at the base of the nipple would reappear, and again suckling would be discontinued. If the cracked nipple recurred repeatedly, sooner or later—sometimes within a few days, and nearly always within a few weeks—a spreading cellulitis in the connective tissue between the lobes of the breast would develop, giving rise to a sector-shaped flushed area of skin with induration of the underlying tissues. A rise in temperature accompanied the local signs. At this stage, one of two things could happen. Less commonly the local and general signs would rapidly decrease, so that in a day or two we could be quite sure that the cellulitis would resolve without suppuration. More often, however, the general signs would persist, and the local signs increase, so that a breast abscess became inevitable. The portal of entry for the bacteria (nearly always a staphylococcus) was a fissure at the base of the nipple, so that the infection occurred most often in the early weeks of the puerperium when cracked nipple was most common; it occurred very rarely when good nursing care was available, because the prevention and early treatment of cracked nipple were more efficient in such circumstances; it was rare in hospital practice, but more common in domiciliary practice; it never occurred in epidemic form. The inflammatory process was manifestly a cellulitis of the interlobular connective tissue; it was never possible to express pus from the ducts of the breast.

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Since the introduction of penicillin this type of mammary cellulitis seldom proceeds past the initial stage, and with chemotherapy the majority of cases resolve in a day or two without suppuration. There is, however, a small (possibly an increasing) number of cases in which the Staphylococcus is penicillin resistant, and if it is also resistant to aureomycin and Chloromycetin, suppuration still sometimes occurs. Until the nineteen thirties this was the only well recognized type of breast infection in England, but during those years a new type of infection came to be recognized in hospital practice.

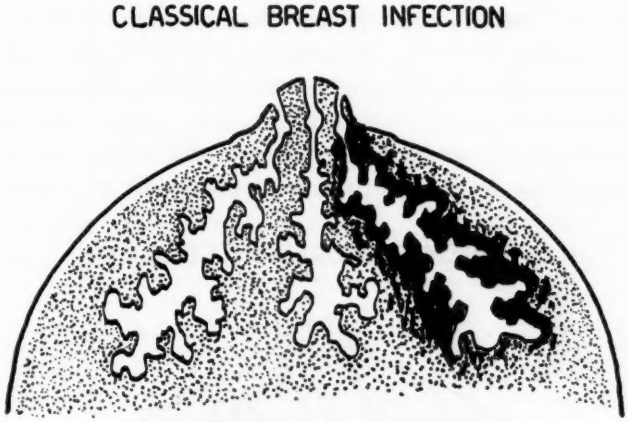

Fig. 1.

2. Acute Puerperal Mammary Adenitis

The most striking feature of this new type of infection was that it occurred in epidemic form, and was, in many cases, associated with an outbreak of skin infections in the infants. A Staphylococcus was the cause. The clinical course of the disease was generally less acute than in the classical type; induration and tenderness were less marked, and constitutional upset less severe. Cracked nipple was not a feature, and the inflammation primarily affected the lactiferous apparatus of the breast, and not the interlobular connective tissue. It was often possible to express pus from the ducts opening on to the nipple. Sometimes several nonadjacent lobes in one breast were affected, suggesting that the infection had gained entrance through more than one duct; sometimes both breasts were involved. The onset was often insidious, and the progress usually tedious. The majority of the cases began in the second week of the puerperium, but sometimes there were not any signs until the mother and her baby had been at home for several weeks. Suppuration generally occurred, but this was often delayed for weeks, and sometimes areas of subacute or chronic induration would break down at intervals of many weeks or months. The condition was rare in domiciliary practice. There were few hospitals which were entirely free. Most hospitals had occasional

small epidemics with two or three cases: a few hospitals had larger outbreaks, and in at least one hospital the proportion of mothers affected rose at one time to 50 per cent.

Since the war these outbreaks have been rare, and I know of no example of epidemics of serious proportions, but an occasional case, or small crop of cases, of this type is still sometimes seen. The Staphylococcus concerned is generally penicillin sensitive, so that in the majority of cases the infection rapidly resolves without suppuration.

The epidemiology of this type of breast infection has been studied in several outbreaks in England, generally with quite inconclusive results. Blaikley and Knott brought forward very strong evidence for believing that the common vector for the Staphylococcus in maternity wards was a nose or throat carrier among the staff, and they have used in vitro tests of virulence of Staphylococci from nasal swabs from doctors and nurses as a basis for control of these infections in the maternity department at Guy's Hospital. It

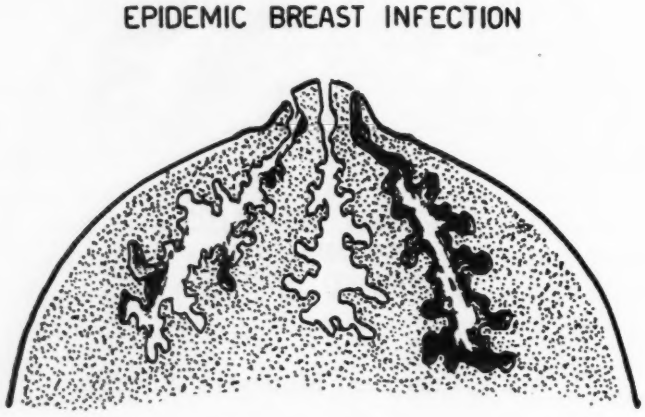

Fig. 2.

happens that no serious outbreak of staphylococcal infections of the breast, or in the infants, has occurred at Guy's since the war; but it is not possible to say how far this happy result is due to the control measures, to the use of effective antibiotics, or merely to good fortune.

A most valuable contribution to the epidemiological aspect of the problem has been made by Colbeck in his study of the Winnipeg outbreak in 1947—an outbreak in which it was possible to follow the natural history of the disease because the Staphylococcus concerned happened to be penicillin resistant, so that the clinical picture was not obscured by treatment. It is not for me to describe the Winnipeg outbreak to my Canadian friends, and they are, of course, quite familiar with Colbeck's findings. But apart from the epidemiology with which Colbeck's paper was chiefly concerned, I think he has made a most important contribution to our understanding of the morbid anatomy of

the disease. Without denying the possible importance of carriers among the staff of the hospital, he has drawn attention to the overwhelming importance of the babies themselves as carriers, and he has suggested a mechanism by which the mother's breast becomes infected. The purpose of my communication today is to point out that, quite apart from epidemiological considerations, there are two entirely distinct types of puerperal breast infection, and that the distinction rests on differences in morbid anatomy that are reflected in differences in physical signs. It is nearly always possible on clinical findings alone to draw a sharp distinction between the classical mammary cellulitis secondary to a cracked nipple, and the epidemic type of mammary adenitis due to a duct infection. Until I had read Colbeck's paper, I had never been able to understand the mechanism of the duct infection that is so characteristic of the epidemic cases. Ascending duct infection is uncommon anywhere in the body, and, in general, it is necessary to have very special circumstances to account for it. Colbeck has shown that in epidemic times the baby's mouth can be a constant reservoir of Staphylococci, and that it is reasonable to suppose that the baby constantly reinoculates the lactiferous ducts of the mother as she suckles it.

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THE TUCKER-McLANE FORCEPS

A History

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(From the Sloane Hospital for Women)

IN THE early days of American obstetrics all of the instruments in use were of European design. Then, as American medicine developed, the ingenuity of obstetrical practitioners increased and subsequently a number of excellent American obstetrical forceps were developed. One of these, the Tucker-McLane forceps, was the product of the efforts of two prominent obstetrical practitioners of the late nineteenth century, James Woods McLane and Ervin Alden Tucker. This instrument is unique in that it is probably the only forceps in common use today which utilizes the solid blade. This feature combined with an overlapping shank and reasonably light construction makes a particularly useful instrument for rotation of the occiput and other obstetrical operations in which a thicker, larger blade would be less suitable.

The characteristic solid blade was not original with Dr. Tucker or Dr. Mclane, for before the middle of the nineteenth century there were at least ten recorded European types of forceps with nonfenestrated blades.[1] In 1850 Dr. Anton F. Hohl[2] of Halle, Germany, described in his text a long-shanked, solid-bladed forceps with a depression on the inside of the cephalic curve of the blade to increase the holding effect. This same feature is found today in the Luikart modification of the Tucker-McLane forceps. In 1860 Dr. Samuel T. Knight[1] of Baltimore, Md., introduced a forceps of his own design with a narrow, nonfenestrated blade. Like many other forceps, this never became popular and soon sank into oblivion.

During the latter part of the same decade, the instrument which was to become known as the Tucker-McLane forceps was conceived by Dr. McLane. This original instrument, which bore Dr. McLane's name, consisted of thin, nonfenestrated blades with a moderate cephalic curve. The shanks were slightly separated and converged on an English-type lock. The ebony handles, which were larger than those of most popular instruments of the day, had prominent shoulders and convenient finger grips.

The date the original McLane forceps was made cannot be determined exactly. However, existing records of George Tiemann and Company[3] of New York, the manufacturers of the original instrument, indicate the first model was made sometime during the year 1868. The first illustration of the forceps appears in Tiemann's catalogue of 1880. Dr. McLane was not a prolific writer and he never published any description of his forceps. The earliest record of the use of the McLane forceps is in 1891 in the first report of the Sloane Maternity Hospital. This report by Dr. McLane[4] describes the first thousand deliveries

at Sloane Hospital. There were 83 forceps deliveries recorded and forceps of "Dr. McLane's pattern" were used in 81 instances for both "high and low operations." The first child born by forceps operation at the Sloane Hospital was delivered by Dr. McLane with his own forceps. This instrument is still preserved in the forceps museum of the Sloane Hospital for Women in New York.

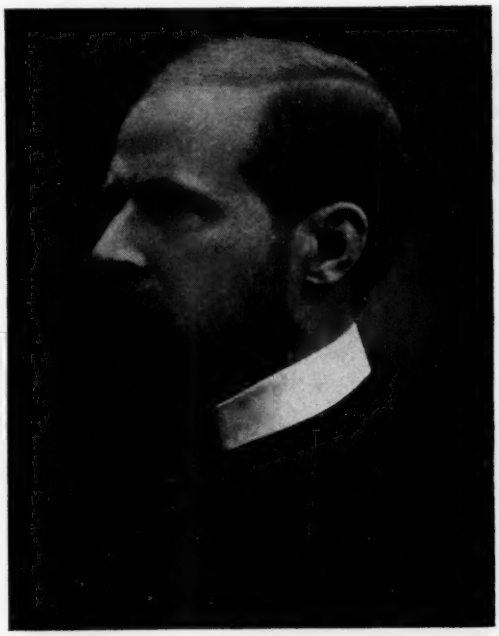

Fig. 1.—James Woods McLane, 1839-1912.

The date Dr. Tucker first modified the original McLane instrument by lengthening the shanks, causing the shanks to overlap somewhat, and changing the handle from ebony to hard rubber is not known. Again, no published or written record of this change was made. However, the date certainly lies between the years 1890 and 1895 while Dr. Tucker was a resident at Sloane Maternity Hospital. Dr. McLane describes the modification in his own words as follows: "Dr. Tucker, a resident physician, thought the shank too short for high operations and had it made slightly longer as seen in the 'McLane-Tucker' instrument." In 1876, R. Olshausen[1] of Berlin described a forceps of his own design with solid blades, long, slightly divergent shanks, and a smooth handle. This instrument closely resembles the present-day Tucker-McLane forceps and it is quite possible that Dr. Tucker's idea for elongating the shanks of the McLane forceps was conceived while he was studying at Olshausen's clinic in 1890.

The changes that Dr. Tucker introduced have been retained and represent the instrument as it is used today.

Subsequent modifications of the Tucker-McLane forceps have been made but are not widely used. In 1910 Dr. George W. Kosmak[5] of New York developed a forceps for outlet use only which used the Tucker-McLane blades inserted directly into the handles, completely omitting the shanks. The same

year Dr. Ellice McDonald[6] of New York modified the Tucker-McLane forceps by cutting from 8 to 15 small transverse fenestra in the blades to prevent slipping with strong traction, since this is probably the greatest defect of the Tucker-McLane forceps. In 1937 Dr. Ralph Luikart[7] of Omaha, Neb., inserted elliptical depressions in the cephalic curve of the blades, also representing an attempt to increase the holding power. This identical feature is found in Hohl's solid blade forceps of 1850. Dr. Arthur Bill[8] of Western Reserve University devised, in 1924, an axis traction apparatus (Bill's handle) which is used on the Tucker-McLane forceps when accurate axis traction is needed for midforceps operations.

Brief biographies of Dr. McLane and Dr. Tucker are in order here as both physicians were outstanding practitioners of their day.

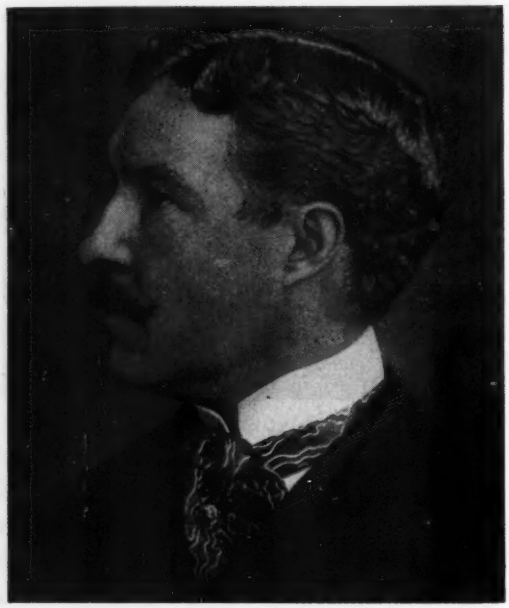

Fig. 2.—Ervin Alden Tucker, 1862-1902.

James Woods McLane[9, 11] was born in New York City Aug. 19, 1839. He received his early education from private tutors and at Phillips Academy, Andover, Mass. He graduated from Yale University in 1861 and immediately undertook the study of medicine at the College of Physicians and Surgeons in New York. He graduated from this institution in 1864 with "more than the average reputation for diligence." Dr. McLane at once entered practice in New York City, and after several promotions was made Professor of Obstetrics and the Diseases of Children at the College of Physicians and Surgeons in 1872, eight years after his graduation. He served in this capacity until 1898 when he became Emeritus. In addition to many professional affiliations, including being the first attending obstetrician of Sloane Maternity Hospital, he was appointed President of the College of Physicians and Surgeons in 1889. He held this position until 1891 when the school became affiliated with Columbia University. He continued after the merger for 12 years as Dean of the Faculty of Medicine. Through his

efforts funds were obtained from William K. Vanderbilt to establish the well-known Vanderbilt Clinic of the Columbia-Presbyterian Medical Center of New York. In addition, he[12] obtained funds from Mr. and Mrs. W. D. Sloane to build the Sloane Maternity Hospital which opened on Jan. 1, 1888. This is now known as the Sloane Hospital for Women and is also affiliated with the Columbia-Presbyterian Medical Center.

In 1898 Dr. McLane retired from active teaching and was succeeded by Dr. E. B. Cragin in the Chair of Obstetrics.

Ervin Alden Tucker[10, 13] was born on Feb. 2, 1862, in Attleboro, Mass. He received his early education in the public schools of Attleboro and in Providence, R. I. He graduated from Amherst College in 1885 with a B.S. degree. He then attended the College of Physicians and Surgeons in New York for 3 years and graduated in 1889 with honors. Following this Dr. Tucker served six months as assistant resident physician at Nursery and Child's Hospital in New York. In December, 1889, he went to Germany to study obstetrics with Olshausen, Dührssen, and others. The following December he returned to New York and became an instructor in obstetrics at the College of Physicians and Surgeons and the sixth resident physician at Sloane Maternity Hospital.

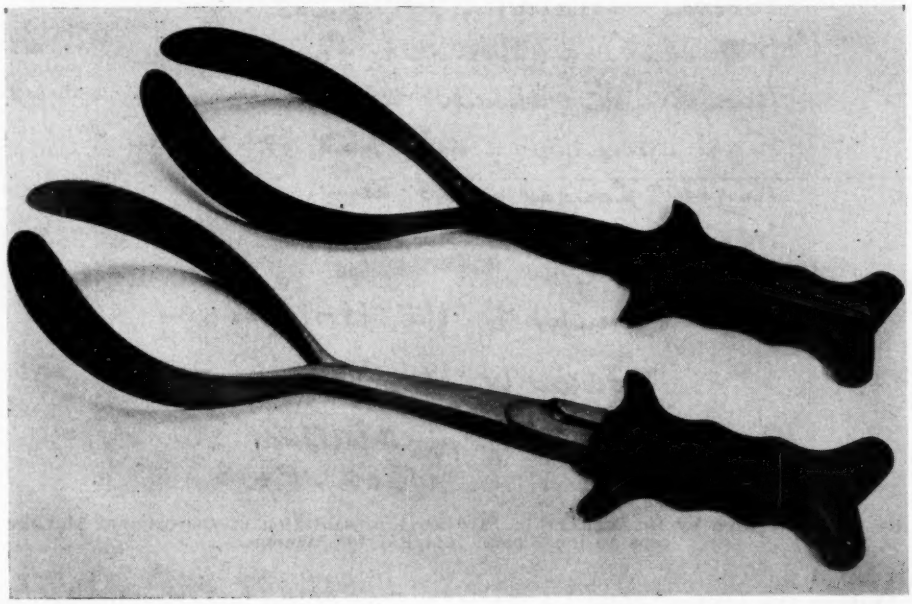

Fig. 3.—The original McLane forceps (above) and a very early model of the Tucker-McLane forceps (below). From the forceps museum of the Sloane Hospital for Women, New York.

From 1890 to 1895 Dr. Tucker had the satisfaction of seeing the Sloane Hospital service increase from 400 to 900 deliveries a year, making it the largest obstetrical hospital in the United States. Besides his modification of the McLane forceps and the improvement of many of the existing obstetrical instruments of the day, he introduced the "cephalic" rather than the then existing "pelvic" method of forceps application. He was planning publication of this now commonly used method in 1902 when he met an untimely end at the age of 40 years.

Dr. Tucker resigned as resident of Sloane Hospital in 1895 and became the first man in New York City to devote himself exclusively to the practice of obstetrics. He was extraordinarily successful because of his ability and had a very large practice.

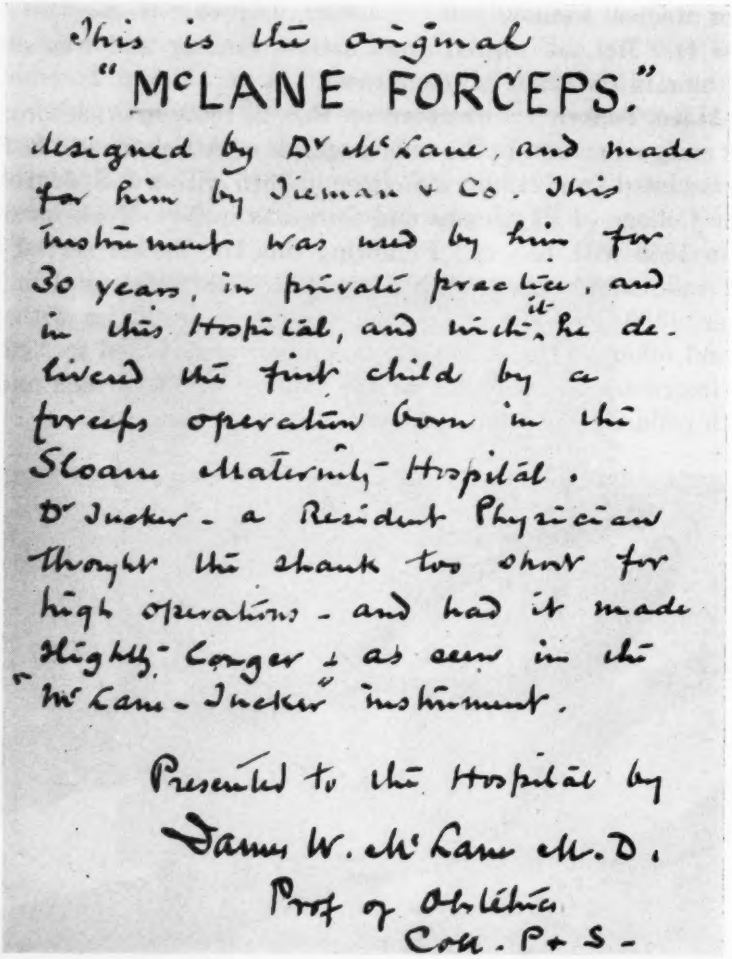
This is the original
"McLANE FORCEPS."
designed by Dr McLane, and made for him by Sieman & Co. This instrument was used by him for 30 years, in private practice, and in this Hospital, and with it he delivered the first child by a forceps operation born in the Sloane Maternity Hospital.
Dr Tucker - a Resident Physician thought the shank too short for high operations - and had it made slightly longer - as seen in the McLane - Tucker instrument.
Presented to the Hospital by
James W. McLane M.D.
Prof of Obstetrics
Coll. P. & S.

Fig. 4.—A note written by Dr. McLane in 1910 upon presentation of the original McLane forceps to the Sloane Hospital for Women.

During the winter before his death Dr. Tucker had been working extremely hard and on the "wretchedly stormy night" of Feb. 25, 1902, he was called to see a patient at two in the morning.[14, 15, 16] His wife begged him to send someone in his place, but he refused. He was unable to procure a cab, for it was "the night of the gala opera performance given in honor of Prince Henry" and he stood twenty minutes on the corner of 59th Street waiting in the storm for a crosstown car. He remained up with his patient throughout the night and next morning he started his rounds after only an hour's sleep. At the home of a patient he had a severe chill, so he excused himself and went home to bed. It was obvious that he was quite ill and he received immediate medical attention from

the best New York physicians, including Dr. Francis Delafield and Dr. Edward C. Janeway. However, lobar pneumonia had become too well established and he never recovered. On the sixth day of his illness, about 11:30 in the evening of March 3, he suddenly became delirious, developed pulmonary edema and died, thus cutting short a brilliant career in its prime.

Dr. McLane outlived Dr. Tucker by ten years and continued in active practice until several years before his death on Nov. 25, 1912.

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TACE (CHLOROTRIANISENE), A NEW ESTROGEN FOR INHIBITION OF LACTATION

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IT IS variously estimated that between 50 and 75 per cent of the babies born today are not breast fed. Absolute medical contraindications to nursing account for a significant number of these cases, while relative contraindications are responsible for others. Improved methods of artificial feeding and the addition of vitamin supplements to the infant's formula have reduced the physician's insistence that all babies should be breast fed and the modern mother, in a changing social and economic era, has given further impetus to the trend toward artificial feeding. Suppression of lactation in the postpartum period has thus become a problem of great clinical importance and the use of estrogenic hormones in this field is now well established.

In 1933 Smith and Smith[1] demonstrated a pronounced decrease or even total disappearance of the mammary secretion in postpartum rabbits as a result of the administration of large amounts of estrin. In 1937 Dodds and Lawson[2] described the estrogenic effects of 4:4′-dihydroxy stilbene and a year later[3] those of the much more potent diethyl derivative now commonly called stilbestrol. This substance, which could be given orally, soon became widely used so that by 1944 there had been publications[4] describing a total of 1,715 cases in which stilbestrol had been employed for the inhibition of lactation and engorgement of the breast.

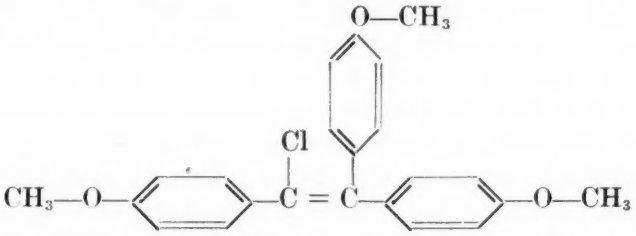
In one large series of cases[5] in which alternate patients received stilbestrol in an attempt to reduce maternal morbidity, 45.3 per cent of the 478 infants in the treated group were adequately breast fed even during stilbestrol administration. The comparable figure in the control group of 485 infants was 74.4 per cent, indicating that stilbestrol has a demonstrable inhibitory influence on lactation, but that in almost half the cases other factors, such as the sucking reflex, can maintain adequate supplies of milk for infant nutrition. Nevertheless, in the majority of cases, satisfactory relief from symptoms associated with breast engorgement in nonnursing mothers has been reported following oral stilbestrol therapy[4] although leakage and return of lactation following cessation of therapy have frequently occurred.[6-10]

Of considerably greater concern is the occurrence of withdrawal bleeding, a blood loss the patient can ill afford, and the possibility that it might delay the detection of real postpartum hemorrhage which requires prompt and sometimes heroic measures. It was recognized as early as 1941[11] that vaginal bleeding occurred in 15 of a series of 120 patients treated with stilbestrol for postpartum engorgement of the breast. In 7 of these patients (5.9 per cent) the post-

partum uterine bleeding was excessive. This frequency was almost exactly duplicated in a series[12] of 1,591 consecutive cases similarly treated from 1948 to 1951 in which the incidence of 6 to 7 per cent was reported. Other investigators[13, 14] have called attention to the alarmingly profuse withdrawal bleeding which may complicate stilbestrol therapy, especially when additional courses of treatment are required for recurrence of breast engorgement after discontinuation of medication.[13] It was then suggested[15] that the inhibitory effect of stilbestrol would be more satisfactory if medication were extended over a longer period of time and then gradually diminished.

A new type of estrogen, TACE,* depends in part for its unique effects upon its property of fat storage.[16] Following oral administration, part of the dose is stored in the body fat from which it is released gradually over a prolonged period of time, leading to a gradual decrease in estrogenic stimulation.[17]

TACE is represented by the following formula:



which chemically is tri-p-anisylchloroethylene. There is a resemblance between it and diethyl stilbestrol and hexestrol in that all three compounds have two phenyl groups separated by two carbon atoms; these carbon atoms are saturated in hexestrol and unsaturated in TACE and diethylstilbestrol. In TACE, however, the two hydroxy phenyl groups of the other two estrogens are replaced by two methoxy phenyl groups and the two ethyls are replaced by a methoxyphenol and a chlorine group.

The occurrence of late bleeding in a relatively large number of his patients who had been receiving ethinyl estradiol in oral dosage of 0.3 to 0.5 mg. daily, prompted Heckel[18] to administer TACE to a series of 18 patients in order to suppress lactation, and to determine whether the slow elimination of TACE would decrease the incidence of withdrawal bleeding. He used TACE in a daily dosage of 48 mg. (1 capsule 4 times daily) for a period of three to five days. There was no bleeding in this small group of patients, and in 16 of the 18 there was a very satisfactory inhibition of lactation and relief from symptoms.

Our experience, after use of various estrogens during a ten-year period to suppress lactation, is consistent with the views expressed in the publication already cited. Encouraged by the results reported by Heckel, we treated a series of 100 consecutive private patients with TACE with a view toward suppressing lactation, increasing the period of treatment to seven days because of the two failures in Heckel's series which may have been due to inadequate dosage.

*TACE is the trade-mark of The Wm. S. Merrell Company, Cincinnati, Ohio, for its brand of chlorotrianisene (tri-p-anisylchloroethylene), which was developed by M. G. Van Campen and R. S. Shelton in the Organic Research Laboratories of this company.

Treatment with TACE was usually instituted on the first day after delivery, but in those cases where a decision to suppress lactation was made later, TACE was started when indicated. There were cases, for example, in which breast feeding was tried but had to be discontinued after periods of 7 to 19 days because of cystic mastitis associated with fever, chills, markedly enlarged indurated breasts, increased local heat, and local adenitis. Contrary to the experience with older estrogens, which are more effective when started early,[15] the time when TACE was started did not seem to influence the gratifying response; accordingly, all 100 cases are considered together. The single course of TACE resulted in symptom-free suppression of lactation in 97 of the 100 cases. Only 3 patients, in whom painful filling of the breasts occurred following the cessation of initial therapy, required a second course of TACE. Two of these started the second course on the tenth postpartum day. One was treated for a period of three days, and the other for four days in a dosage of four capsules daily. The remaining patient required her second course on the twelfth postpartum day and was treated for seven additional days. From our experience and published reports it would appear that TACE is possibly even more effective than stilbestrol in the initial suppression of lactation. However, recurrence of symptoms is much more frequent after stilbestrol. Only 3 per cent of the TACE-treated patients required a second course, while the highest comparable figure published for stilbestrol indicates that 41 of 53 patients,[6] or 77.3 per cent, required additional treatment with that estrogen.

Of considerably greater potential importance is the virtual absence of postpartum bleeding in the TACE group. This was limited to 1 in the series of 100 cases and it was extremely scant, occurring on the tenth postpartum day in a patient who also had a recurrence of breast engorgement and then received additional TACE therapy for four more days. This is an incidence of 1 per cent to be compared to 6 per cent of 1,711 reported cases on stilbestrol.[11-12] These figures have been subjected to the usual statistical analysis and the lower incidence of bleeding in the TACE group as compared to the stilbestrol group is significant.*

Summary

TACE is a new estrogen which is highly effective in the suppression of postpartum lactation when given orally in dosage of 48 mg. (4 capsules) per day for seven days. Recurrence of symptoms and appearance of withdrawal bleeding are virtually eliminated, probably because of the storage of TACE in the body fat and its gradual release after cessation of therapy.

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*The value for chi square is 4.4 and $p = 0.035$.

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CLINICAL EVALUATION OF METHYLERGONOVINE TARTRATE (SEMISYNTHETIC ERGONOVINE)

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DURING the past eight years several papers have appeared in the American literature relating to the effectiveness of the synthetically prepared oxytocic, methylergonovine tartrate (Methergine*). Its importance as an oxytocic agent becomes increasingly evident since the world sources of crude ergot of high alkaloidal content are limited.

Many previous studies have compared favorably the action of Methergine with that of natural ergonovine. Gill[1] reported on his use of an intrauterine bag connected to a manometer to compare accurately the oxytocic effects of Methergine and ergonovine in postpartum patients. He found that such uterine contractions were 1.5 times stronger and 1.3 times of greater duration with Methergine. Kirchhof and his associates[2] have reported upon extensive studies on the oxytocic activity of Methergine on the uterus and on the sympathetic nervous system.

The average duration of the third stage of labor following use of methylergonovine tartrate was shortened in the experience of many observers. Tritsch, Schneider and Longworth[3] reported an average length of the third stage from delivery of the anterior shoulder to delivery of the placenta of 6.9 minutes, Roberts[4] reported 4.3 minutes, and in 87 per cent of Schade and Gernand's[5] series of cases, delivery of the placenta occurred in five minutes or less.

Several studies on the comparative effectiveness of Methergine and ergonovine have been reported, including those by Cartwright and Rogers,[6] Schade and Gernand,[5] Riordan and his co-workers,[7] and others.[8-11] In general, all have reported favorably upon the use of the semisynthetic compound in terms of total blood loss, absence of systemic side effects, and the length of the third stage of labor.

Brougher[12, 13] and Farber[14] have reported upon their use of the drug for induction of labor. In small series of cases they both found Methergine to be a safe and effective agent for this purpose.

Material

The present study was done on 309 private patients of four obstetricians practicing in northern New Jersey. No selection was attempted and, so far as such a limited series permitted, all types of patients were included. Blood loss during the course of the delivery was actually measured in 64 cases, estimated as accurately as possible in 245 cases. In all instances blood absorbed

*Methergine supplied by Sandoz Pharmaceuticals, New York 14, N. Y.

in drapes and sponges was taken into consideration in estimating blood loss. No differentiation between blood loss from the episiotomy and that from the uterus was made but the former was kept to a minimum by appropriate measures. Routine episiotomy was performed in all but a few instances.

Routinely 1 ampule of Methergine (0.2 mg.) was administered by vein following delivery of the anterior shoulder in 285 cases and after the birth of the baby in 24 cases. In 17 cases it was given intramuscularly. Following this the baby was delivered very slowly over a 30- to 60-second period.

The majority of the patients (245 cases) were primigravidas or had had but one previous delivery (79.2 per cent). The method of delivery is included as Table I. Toxemia was present in 13 cases (4.2 per cent) of which 9 were pre-eclampsia, 4 were hypertensive.

TABLE I. METHOD OF DELIVERY

METHOD	NO. CASES	PER CENT
Normal delivery	113	36.5
Low forceps (elective)	166	53.7
Low forceps (indicated)	13	4.2
Midforceps	3	0.9
Breech delivery	5	1.6
Cesarean section	9	2.9

Anesthesia generally was by inhalation and the most frequently employed combination was cyclopropane and oxygen (50.4 per cent). All cesarean sections were low cervical in type and were performed with but one exception under spinal anesthesia.

Results

The average blood loss during the third stage of labor was 119 ml., the minimum blood loss being 25 ml., the maximum 650 ml. (Table II). Additional medications such as Pitocin and natural ergonovine were employed in 19 cases.

TABLE II. BLOOD LOSS DURING THIRD STAGE OF LABOR

BLOOD LOSS IN ML.	NO. CASES	PER CENT
0-50	52	16.8
51-100	129	41.7
101-200	113	36.5
201-400	9	2.9
over 401	6*	1.9
Average blood loss—119 ml.		

*Five patients in this group were delivered by cesarean section.

The average duration of the third stage (from time of complete delivery of the baby to expulsion of the placenta) was 4.8 minutes.

The placenta required manual removal in 9 cases. In 7 of these the placenta was found to be incarcerated in the cervix and was readily released. In two instances the placenta was wholly or partially adherent to the uterine wall. In one of these there was a sizable succenturiate lobe present.

A group of patients were followed with frequent blood pressure readings prior to and just after administration of the oxytocic. In 6 cases out of a total of 73 normal patients studied, the systolic blood pressure was increased by a maximum of 18 mm. mercury. There was no significant increase (less than 10 mm.) in the other 67 cases. In the 13 patients who had toxemia, the systolic pressure was elevated in 9 instances by a maximum of 14 mm. mercury. In 4 cases there was no significant rise. Thus Methergine exerted but little vasopressor action in the group under observation.

Methergine tablets were used routinely in this series, generally being administered by mouth at 4 hour intervals for a total of 6 doses during the early puerperium. A large group of patients (71 per cent) complained of uterine cramps, which was in about the same proportion as other observers have reported following use of natural ergonovine.[10] Headache was experienced by 22 per cent of patients who received the drug. The uterus involuted normally in all instances. There were no delayed postpartum hemorrhages, with one exception. This patient later required a curettage because of retained secundines. The usual hospital stay following delivery ranged between 5 and 9 days, and averaged 5.3 days.

Labor was induced successfully in a small number of patients at term with intact membranes with the use of Methergine. This will be reported upon in a later paper.

Summary and Conclusions

1. Methylergonovine tartrate (Methergine) has been employed in a series of 309 private patients under controlled conditions.

2. Following intravenous or intramuscular administration of the drug, the third stage of labor was markedly shortened, the average being 4.8 minutes.

3. Blood pressure rise following use of the drug did not exceed 18 mm. mercury in any case, whether normal or toxic. Rises of more than 10 mm. mercury were observed in 15 cases.

4. The average blood loss during the third stage and the immediate postpartum period was 119 ml.

5. The drug was demonstrated to be rapid in action, dependable, and a safe oxytocic.

6. No sensitivity to the drug was noted and no undesirable systemic side effects were experienced when the drug was given intravenously, intramuscularly, or orally.

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ATTEMPTED PRODUCTION OF ECLAMPSIA-LIKE SYNDROME IN PREGNANT RATS

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THE multiplicity of theories regarding the etiology of eclampsia indicates that little is known about its pathogenesis.[1] Recently an eclampsia-like condition was reported in pregnant rats injected with progesterone.[2] The present report is concerned with an attempt to confirm this result, as an initial step in a proposed program designed to explore this syndrome further.

Experimental

Experiments were carried out on several series of albino rats of an inbred Wistar strain. The rats, weighing approximately 200 grams, were injected intramuscularly with a total of 20 mg. of progesterone (Schering's Proluton,* 5 mg. per cubic centimeter or 25 mg. per cubic centimeter) in divided doses in the late stages of pregnancy. Concomitantly, similar doses of the hormone were administered to a group of nonpregnant female rats. As a further control procedure a volume of sesame oil equal to that containing the progesterone was injected into a group of pregnant control rats.

Dog Chow pellets supplemented with fresh carrots were fed and water was given ad libitum during the course of these experiments.

Series I.—Two rats were injected intramuscularly with Schering's Proluton, 5 mg. in 1 c.c. of sesame oil, half in each hind leg on the fifteenth, sixteenth, seventeenth, and eighteenth days of pregnancy. At the same time three nonpregnant controls were given the same treatment.

Series II.—This series, which consisted of sixteen pregnant rats and five nonpregnant ones, received the same dose as those in Series I, except that the volume of the injection was 0.2 c.c. instead of 1 c.c.

Series III.—This group received 10 mg. of progesterone daily by the intramuscular route on the seventeenth and eighteenth days of pregnancy. There were two pregnant and 3 nonpregnant rats in this series.

Series IV.—Three pregnant rats were injected intramuscularly with 1 c.c. of sesame oil on the fifteenth, sixteenth, seventeenth, and eighteenth days of pregnancy.

Results

Under these conditions an eclampsia-like syndrome could not be produced in pregnant rats injected with progesterone. All animals appeared normal and healthy throughout the course of the experiments. All the rats delivered at the estimated date of confinement with the exception of two in Series II, which were sacrificed on the twenty-seventh and thirtieth days after mating. No abnormalities were noted microscopically in the fetuses or placentas, or in

*We wish to express our thanks to the Schering Corporation for this gift.

the mothers' livers or kidneys. An autopsy was performed on five additional mothers in Series II soon after delivery. Grossly and microscopically no lesions were found in the liver or kidneys. In the remaining rats observation for several months revealed no impairment in fertility and the future pregnancies terminated normally. No untoward effects were noted in the control groups.

Comment

In attempting to reconcile these negative results with those of Symeonidis[2] it should be pointed out that an inbred Wistar strain was used in the present experiments whereas Symeonidis used the inbred Marshall 520 strain. In all other respects the experimental conditions were the same. Whether or not the difference in strain accounts for the disparity in results is questionable. Assuming that such a seemingly insignificant feature is the basis for our lack of agreement, it would appear unlikely that positive results could be obtained in a different species of experimental animal. The relationship of such data to human toxemia of pregnancy would appear even more remote.

As a corollary to these experimental results, progesterone is usually not implicated clinically as a factor in producing pre-eclampsia. Low values for urinary pregnanediol in toxemic pregnancy[3, 4, 5] have been reported. Bachman[6] has studied the urinary excretion of this steroid in pre-eclampsia and chronic hypertensive vascular disease of pregnancy, and has found that an abnormally low excretion was invariably associated with proteinuria. It remains to be determined whether the abnormally low level of urinary pregnanediol excretion reported in the toxemias is the result of renal retention, or abnormal metabolism, or of low placental production of progesterone.[7]

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PENICILLIN ADMINISTERED VAGINALLY AND ORALLY: COMPARISON OF PLASMA CONCENTRATIONS AND URINARY RECOVERIES

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THE administration of 100,000 or more units of penicillin by the vaginal route can produce an assayable penicillemia.*[1, 2, 3] Similarly, therapeutically effective plasma concentrations can be obtained consistently following oral administration of penicillin in a dose of at least 100,000 units,[4, 5, 6, 7] and there is ample justification for employing this route of administration for systemic therapy.[8, 9] It therefore seemed purposeful to compare in the same subjects and under strict experimental conditions the plasma concentrations and urinary recoveries of penicillin obtained after the intravaginal and oral administration of the antibiotic agent.

Methods

Ten women with no known genitourinary or gastrointestinal disease were studied. Those in the menstrual era were studied without regard for the menstrual cycle except for the avoidance of menstruation. Their ages varied from 31 to 68 years, their weights from 108 to 151 pounds.

All subjects were studied after 8 hours of fasting. In the first phase of the investigation, the subjects ingested 200 ml. of water and two tablets* each containing 100,000 units of potassium penicillin. In an effort to eliminate any variable influence of posture on renal blood flow, the subjects remained supine for the 3 hours of observation, without ingesting food or fluids. At intervals of ½, 1½, and 3 hours after the administration of the penicillin, 10 ml. of venous blood was withdrawn into heparinized syringes for penicillin assay. Blood samples were centrifuged and the plasma pipetted into sterile vials. At the end of 3 hours the subject was catheterized, the urine volume measured, and an aliquot kept for estimation of the urinary excretion of penicillin during the 3 hour period. Forty-eight hours later the same subjects were again studied. With the subject in the dorsal lithotomy position in bed, a vaginal speculum was inserted and the cervix exposed. The approximate pH of the posterior vaginal fornix was determined with nitrazine paper. The cervix and posterior vagina were then wiped with absorbent cotton. Two 100,000 unit tablets of penicillin, from the same lot previously used, were inserted in the posterior vaginal fornix and the speculum carefully withdrawn. The subjects again remained supine for the period of observation. Blood and urine specimens were obtained as previously described. Plasma and urine specimens were refrigerated at minus 20° C. within 30 minutes after collection and held until assayed. Penicillin assays were done by the Rammelkamp serial dilution method (using *Streptococcus hemolyticus* strain 98 and group 0 human red blood cells).

*Penicillemia is a synonym for the cumbersome phrase "penicillin plasma concentrations" that has been coined by one of us (W. P. B.).

Results

The average blood levels obtained for the 10 subjects 1½ and 3 hours after the vaginal administration of penicillin were statistically significantly higher† ($P > .02 < .05$) than those found following oral administration (Fig. 1). The level at ½ hour, although also higher than that following the oral route, was not statistically so ($P > .1$). The individual values obtained for each subject are given in Table I. Seven of 10 subjects showed at ½ hour plasma concentrations of penicillin that were higher after vaginal than after oral administration. All 10 patients had higher degrees of penicillemia at 1½ and 3 hours after vaginal administration than following ingestion of the antibiotic. All 10 patients, when given penicillin intravaginally, maintained a penicillemia above the commonly accepted "therapeutically significant" concentration of 0.03 unit per milliliter throughout the 3 hour period of observation.

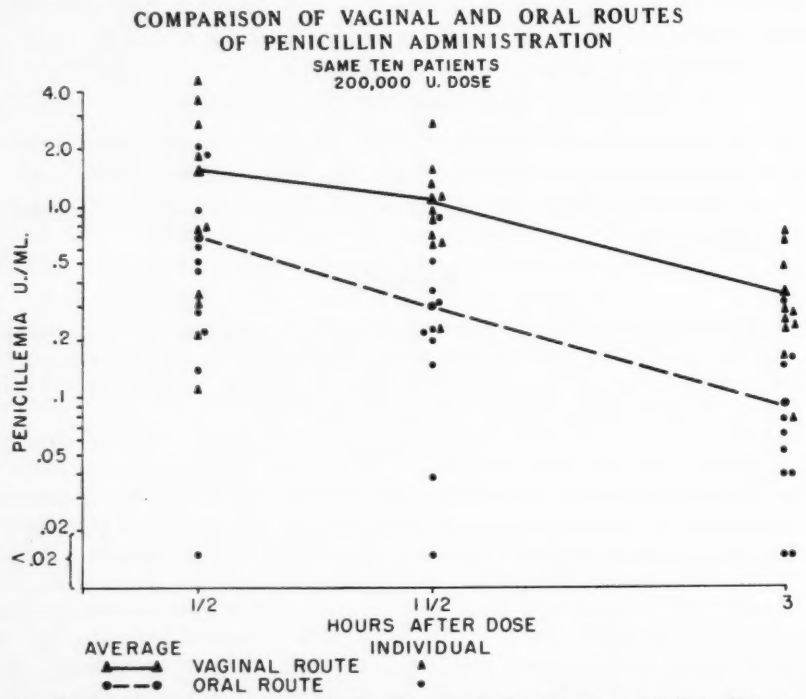

Fig. 1.—Comparison of the individual values and the averages of the plasma concentrations of penicillin observed in 10 women following the intravaginal administration (▲ – ▲) of 200,000 units of potassium penicillin with the average level obtaned in the same 10 subjects following the oral administration (● – ●) of the same dose of penicillin. The average obtained after the intravaginal route is significantly higher than that following oral administration and is well above the "therapeutically significant" concentration of 0.03 unit per milliliter throughout the 3 hour period of observation.

The average of the individual urinary recoveries of penicillin during the 3 hour observation period after ingestion of oral penicillin was 18.6 per cent, a figure in good agreement with those reported in the literature.[5, 6, 7, 10] The recovery following the vaginal administration of the same doses of penicillin to the same patients was 31.4 per cent. This figure compares favorably with that of 6 to 28 per cent reported by others.[2] The differences between individuals are demonstrated by the widely divergent urinary recoveries of penicillin and degrees of penicillemia.

*Penalev (Sharp & Dohme Inc.) soluble tablets of penicillin were used throughout this study.

†Student "t" test.

Comment

Under the conditions described, higher penicillin plasma concentrations were obtained after vaginal than after oral administration of penicillin. It seems reasonable to suggest that the vaginal route of penicillin administration might be employed under specialized conditions as a therapy for systemic infections. The ease and practicality of administering penicillin per vaginam may be questioned, but this route has the advantage of avoiding hypodermic needles, which must be increasingly recognized as a means whereby homologous serum jaundice[11, 12] and perhaps other diseases are transmitted.

TABLE I

SUBJECT	AGE (YEARS)	VAGINAL pH	ROUTE	PLASMA PENICILLIN LEVEL (UNITS/ML.) ½ HR.	1½ HR.	3 HR.
M.J.	32	5.0	Oral	.61	.20	.039
			Vaginal	.75	.70	.25
D.B.	38	6.0	Oral	<.019	.156	.078
			Vaginal	1.8	.624	.156
A.E.	62	7.5	Oral	.468	.234	.039
			Vaginal	3.6	.94	.078
M.C.	55	6.0	Oral	.14	<.023	<.023
			Vaginal	.21	.23	.23
H.R.	31	6.0	Oral	.23	.039	<.019
			Vaginal	.31	.62	.23
A.N.	68	7.0	Oral	.52	.22	.052
			Vaginal	2.7	1.58	.27
S.C.	43	4.5	Oral	.95	.52	.16
			Vaginal	.79	.87	.29
F.Y.	56	7.0	Oral	.28	.31	.063
			Vaginal	4.52	2.70	.48
S.G.	37	5.0	Oral	1.88	.88	.31
			Vaginal	.11	1.09	.71
M.K.	39	5.0	Oral	2.00	.37	.15
			Vaginal	.34	1.33	.67
Average			Oral	.71	.30	.09
			Vaginal	1.51	1.07*	.34*
			P	>.1	>.02 <.05	<.01

*Statistically significantly higher than oral (t test).

Oral penicillin therapy is accepted as being effective for the treatment of routine penicillin-susceptible infections. From the data here presented, the vaginal route of penicillin administration would appear to be equal, or even superior, to the oral route with respect to producing detectable penicillin concentrations. The observations emphasize the fact that when penicillin is placed in the vagina for "local therapy," the antibiotic is rapidly absorbed and the resulting penicillin plasma concentrations are sufficiently high as to constitute effective therapy for many systemic infections. Thus, although the indication for treatment is a "local" condition, the therapy administered at the site of infection is in fact "systemic" as well as "local" therapy. The future benefits of using penicillin in the treatment of systemic infections are being denied to many patients by the thoughtless use of "local" therapies in the form of penicillin-containing lozenges, nose-drops, and ointments that

sensitize patients to penicillin; thus, the general effects of intravaginally applied penicillin should be considered before it is employed for "local" therapy.

Summary and Conclusions

Penicillin plasma concentrations following vaginal and oral administration of 200,000 units of penicillin have been compared under standardized conditions. The intravaginal route resulted in statistically significantly higher plasma concentrations. The average urinary recovery of penicillin in a 3 hour period was 18.6 per cent of the oral dose and 31.4 per cent of the vaginally administered dose.

Penicillin administered vaginally is rapidly absorbed and can produce a penicillemia that is adequate for the treatment of many systemic infections. Vaginally administered penicillin should be regarded as both "local" and "systemic" therapy and should not be employed indiscriminately. Failure to recognize the significant absorption of penicillin from the vagina may contribute to the development of penicillin sensitivity and thus deny patients the benefit of systemic therapy with this agent at some subsequent time.

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PSEUDOHERMAPHRODITISM

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THE initial problem in a discussion of pseudohermaphroditism and hermaphroditism is to give an adequate definition of these terms. As stated by Wilkins, it is a morphological rather than an etiological classification of terms.

Pseudohermaphroditism is a condition found in either the male or the female. It is a disorder which is congenital in origin. It is to be excluded from various disorders such as gynecomastia, pituitary and adrenal hirsutism, and secondary sex changes which might occur with the ovarian masculinizing tumor, arrhenoblastoma.

A male pseudohermaphrodite is one who has an ovary but male development of some of the genitals and perhaps some male secondary sex changes.

Using the terminology of Kebs and Neugebauer, pseudohermaphrodites may be classified still more closely. Two of the five adjectives are used in this classification. The first two, masculine and feminine, refer to the status of the gonads. The last three adjectives, internal, external, and complete, describe where the genitals of the individual differ in sex from the gonad.

In the complete type both the internal and the external gonadal structures are abnormal (Table I).

TABLE I

Female Pseudohermaphrodite.—
Feminine gonad, ovary
1. Internal: male vestigial remnants, Gartner's ducts, rudimentary prostate, vas deferens
2. External: external organs resemble male
3. Complete: combination of 1 and 2

Male Pseudohermaphrodite.—
Masculine gonad, testes
1. Internal: tubes, uterus
2. External: undescended testes, genitals resembling female
3. Complete: combination of 1 and 2

Williams states that female pseudohermaphroditism is frequently associated with adrenal cortical hyperplasia and at times adrenal cortical tumors. The male pseudohermaphrodite generally has normal adrenal glands. It is generally accepted that pseudohermaphroditism is congenital in origin; therefore, if a female pseudohermaphrodite is not recognized at birth by an enlarged clitoris or other abnormalities and the question does not arise until a later date, the problem in diagnosis may then be difficult. The difficulty arises in trying to decide whether the individual is a female pseudohermaphrodite, has an acquired adrenogenital syndrome, or has a combination of the two disorders.

True hermaphroditism is a different disorder. The true hermaphrodite is understood to be one possessing both ovary and testis, gonads of both sexes. The classification of hermaphroditism by Creevy is as follows:

1. Bilateral, ovary and testis on each side
2. Unilateral, ovary or testis on one side and both on the other (unilateral ovotestis)
3. Mixed, the most common variety, which presents on each side one gonad which possesses both testicular and ovarian elements (bilateral ovotestes)

A true hermaphrodite would be an individual who is able to fertilize and conceive. This predisposes the necessity of a set of normal male and female organs. Although this does occur in lower animals, it does not occur in man. In cases reported of true hermaphroditism, either the testis or ovary is found to be without function. A term that could be used to describe an individual with a functioning ovary and testis would be an absolute hermaphrodite.

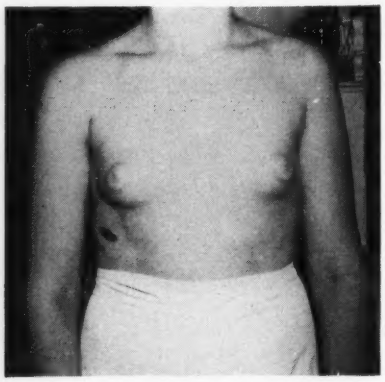

Fig. 1.

Te Linde states that dysgerminomas, which are felt by Meyer to arise from undifferentiated cells that are present in early undifferentiated gonads, frequently occur in women with some degree of sexual immaturity or in real pseudohermaphrodites.

The incidence of pseudohermaphroditism and hermaphroditism is rare. Neugebauer found 50 cases in 52,000 patients. One definitely proved case in 20,523 autopsies was reported from the University of Minnesota. In 1937 Young reported 28 cases of hermaphroditism.

Gunther states that internal pseudohermaphroditism comprises only 10 per cent of all cases.

It is felt that in the older literature many of the diagnoses of pseudo- and true hermaphroditism were mistaken because of the lack of clinical data concerning growth and development, development of secondary sexual characteristics, lack of biopsies, autopsies, and hormonal studies.

Zondek claims that a new hormone which he calls "hormone X" is found in excessive quantity in pseudohermaphrodites. This finding presents a unique differential point in pseudohermaphrodites and true hermaphrodites.

Treatment is dependent on the nature of the individual. Biopsy of the gonads is the only true determining factor.

Plastic procedures may prove to be of great value in external types. This is done in the female by removing the barriers which prevent normal sexual relations and in the male by freeing the penis and repairing a hypospadius which is often present. Undescended testes should be repaired early before puberty which increases the chance of fertility.

Psychiatric care may be necessary if the patient realizes he is sexually abnormal. Depressions and suicide may be the result in these individuals. In certain cases, if the individual has the external genitals and secondary characteristics of one sex and has been brought up as of that sex, it may be safer for the benefit of the patient's well-being to forget the gonad.

Case Report

M. A., aged 6 years, was admitted to the hospital complaining of right lower quadrant pain for three months. The pain was moderately severe and would recur every two to three days, and was associated with either nausea or vomiting. Further history by systems was noncontributory.

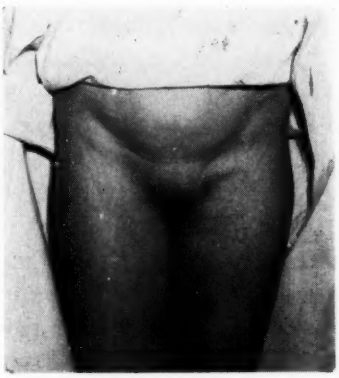

Fig. 2.

Physical examination revealed a well-developed white girl of six years. There were no apparent abnormal physical findings with the exception of tenderness on deep pressure in the right lower quadrant. The impression was that of chronic recurrent appendicitis.

A laparotomy was performed by Dr. Eugene Chesrow on Aug. 7, 1939, under general anesthesia. A midline incision was made and the appendix was removed with inversion of the stump with a purse-string suture. It was noted that the uterus, tubes, and ovaries were absent. The internal rings were open on both sides and the canal contained what appeared to be undescended testicles. The right inguinal ring was repaired after the contents were removed.

Vaginal examination at this time revealed the hymen to be absent. The vagina terminated in a blind sac.

Microscopic examination of the removed tissue revealed immature seminiferous tubules in a very loose areolar structure. No definite evidence of epididymus could be found. The diagnosis was testicular tissue and acute appendicitis.

A left hernia repair was done on Aug. 17, 1939. The left testis was removed at this time.

At the present time, at the age of 20 years, the patient appears to be a normal young woman in appearance and behavior and is desirous of marriage.

Since receiving estrogen therapy for the last twelve months, she has developed a small amount of axillary and pubic hair, and the breasts, although small, have enlarged (Figs. 1 and 2). The vagina admits the index finger and is 6 cm. in depth. The external genitals appear to be infantile in development. Rectovaginal examination reveals no palpable uterus or adnexa.

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DOES MENSTRUAL BLOOD CONTAIN A SPECIFIC TOXIN?*

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THE purpose of the menstrual phenomenon is by no means clear. Robert Meyer suggested that menstruation is the abortion of the unfertilized ovum, a frustration of nature, and, in a sense, a pathological process. He felt that the changes which occur in the uterine endometrium during the course of the normal ovulatory cycle were directed toward pregnancy rather than toward menstruation. In contrast to this is the age-old concept that menstruation is necessary for the cleansing of the female body and that toxic products are eliminated in the menstrual blood. Gautier[1] and Bourcet[2] identified the inorganic poisons, arsenic and iodine, in menstrual excretions and Schiff noted the case of a menstruating woman who caused flowers to wither if she held them in her hand. Macht[3] reported similar observations.

The numerous writings of Smith and Smith[4] furnish important support for the latter point of view. They found that menstrual blood contains a toxin so potent that 0.05 to 0.2 c.c. of whole menstrual discharge would kill 19- to 24-day-old rats within 18 to 48 hours after a single subcutaneous injection. After this material was centrifuged, a lethal dose of toxin was contained in 0.1 to 2 c.c. of supernatant serum or in 0.005 to 0.1 c.c. of washed endometrial debris suspended in saline, inferring that the endometrial debris was the source of the toxin. This finding appeared to be confirmed by the observation that 50 to 100 mg. of fresh endometrium, obtained directly from the uterus just before or during menstruation, was lethal to rats, whereas 200 to 300 mg. (wet weight) of endometrium taken at other times was nontoxic. The extreme potency of menstrual toxin was evidenced by the high incidence of death in female rats, 35 of 37 animals (95 per cent). This lethal effect was enhanced by the simultaneous injection of estrogenic hormone (0.05 gamma estradiol).

Further investigation of this substance led these authors to the conclusion that their toxin was identical with necrosin, the material Menkin found in the pleural exudate of dogs following the inflammatory reaction caused by turpentine. The toxin could be salted out with ammonium sulfate in the euglobulin fraction but, since it did not behave in every respect as a serum euglobulin, it was considered to be an atypical euglobulin.

Smith and Smith feel that this toxin plays an important role in the female reproductive system. They attribute the exaggeration of menstrual molimina, such as premenstrual tension, to prolonged general absorption of the toxin from a secretory endometrium before its disintegration, and the spasm of primary dysmenorrhea to an exaggerated local effect of the toxin. It is pre-

*Read before the Endocrine Society of Philadelphia, Pa., Oct. 14, 1952.

sumed to be the precipitating factor which causes débridement of the endometrium, acting at the same time as a stimulus to the production of gonadotrophins and adrenocorticotrophins by the anterior lobe of the pituitary gland. In this way it induces the normal development of the succeeding menstrual cycle. In addition, the toxin was found to be increased in the blood of patients with toxemia (pre-eclampsia and eclampsia). The conclusions of these authors are best expressed in their own words, "We think that menstrual toxin is the precipitating cause of toxemia as well as menstruation."

Because of the obvious importance of their conclusions, I attempted to confirm these observations but was unable to do so. I reported these discrepancies to Smith and Smith who asked me to announce the results of my experiments in their report[5] at the Laurentian Hormone Conference in September, 1951. In contrast to their observations, we noted a death rate not of 95 per cent but of only 5 per cent in our infantile rats although we injected some with larger doses than did the Smiths. The mortality following the injection of menstrual plasma was, in fact, no greater than after the injection of other tissue extracts such as sow's ovaries, and was less than that following the injection of uncatheterized urine. We were careful to protect the menstrual blood, as far as possible, from contact with the rich bacterial flora of the vagina and to this end introduced a sterile vaginal speculum (tube) at the onset of menstruation and collected blood for 1 to 3 hours. Smith and Smith, on the other hand, employed a rubber balloon which remained in place as long as 24 hours allowing for heavy bacterial contamination.

If we did not collect the menstrual blood as described or if longer periods of time were allowed to elapse, the incidence of mortality in the experimental animals was as high as 60 per cent, suggesting that a bacterial factor might be the important one. The administration of 0.06 gamma or more of estradiol with the menstrual blood did not influence our results and we were unable to detect the presence of a toxic substance in up to 200 mg. wet weight of premenstrual or menstrual endometrium, either alone or with added estrogen.

In spite of our efforts to diminish bacterial contamination of menstrual blood, 5 per cent of our experimental animals died after injection. This was reminiscent of the 7 per cent mortality we had while working out the pregnancy reaction. We thought,[6] at that time, that a toxin was present in some urines which we were removing with ether but subsequently realized[7] that the ether-sterilized urines were contaminated with bacteria (Proteus). Consequently, it seemed possible that the experimental animals which died after injection of endometrial blood might be suffering from the effects of bacteremia rather than toxemia. Accordingly, specimens which had previously been lethal and contaminated were extracted with ether, whereupon they lost their toxicity and were sterile.

In order to check the matter in a different fashion Professor J. Gurevitch, head of the Department of Clinical Microbiology of the Hebrew University-Hadassah Medical School, cultured specimens of menstrual blood and found them to be contaminated—most of them heavily—with *Staphylococcus albus* and *Staphylococcus aureus,* anhemolytic Streptococcus, *Streptococcus fecalis,*

Escherichia coli, Klebsiella pneumoniae, and Lactobacilli, and the longer the blood was in contact with the vagina the greater was the bacterial count. Cardiac blood was removed under sterile precautions from experimental animals which appeared toxic 20 to 48 hours after injection of menstrual blood and cultures were made from the heart blood. The same organisms were found as in the injected menstrual blood (especially anhemolytic Streptococcus, *Staph. aureus,* and *E. coli*).

It therefore seemed certain to us that these experimental animals were dying of infection and not of toxicity, and the next step appeared to be the simultaneous administration of an antibiotic with the menstrual blood in an attempt to protect the rats. Accordingly, 10,000 units of crystalline potassium penicillin G and 5 mg. of streptomycin were given one hour before the injection of menstrual blood, 2 additional times that day, and 3 times the following day. This therapeutic regimen succeeded in avoiding the lethal effect of the injection of menstrual blood.

When informed of the results of this last experiment, Smith and Smith repeated this procedure and confirmed our observations, but drew conclusions which were different from our own. They concluded that penicillin has antitoxic capabilities which are distinct from its antibiotic properties and that penicillin neutralizes the menstrual toxin. If this were the case, and if the menstrual toxin is necessary for menstruation to occur then it should be possible to inhibit menstruation by means of penicillin. That this is not so was demonstrated by 16 healthy women with normal menstrual cycles who were given penicillin in total doses of 2.8 to 7 million units (75 per cent as procaine penicillin G and 25 per cent as crystalline potassium penicillin G) from 4 to 7 days premenstrually to the day of bleeding. In no instance was there any delay or scantiness in the menstrual bleeding and in 4 instances the flow came on 2 days earlier than anticipated. Olansky and R. Hertz have previously noted that menstruation occurs more frequently than usual following massive penicillin administration.

Regarding the importance of the menstrual toxin in the etiology of toxemia of pregnancy, Smith and Smith[8] treated 8 toxemic patients with penicillin and terramycin and concluded that their results were favorable. In addition to the antibiotics, they employed other accepted therapeutic measures such as bed rest, diet, sedation, and glucose. In 2 instances the fetuses died. It seems likely that the coincident placental death allowed improvement to occur since it has been shown repeatedly that toxemia disappears with fetal death even if no treatment is given. In 3 out of 8 cases the pregnancies had to be terminated by cesarean section, with the inference that the penicillin had at best only a transient effect. We have been forced to do a cesarean section in only 5 of 110 cases of severe toxemia managed in the usual ways and without antibiotics.

We have treated 3 toxemic patients* with penicillin and terramycin but could not convince ourselves that any additional benefit accrued from the use

*In the meantime we have treated another 3 toxemic patients with penicillin without any specific result.

of the antibiotics. The condition of one patient actually deteriorated on this therapeutic regimen but this was likely pure coincidence. It should be maintained that antibiotics are beneficial in cases of shock and hepatic coma due to neutralization of endogenous bacterial toxins. A favorable response in eclampsia, if it occurred, might be explained in the same manner.

Summary

1. Menstrual blood, when obtained under relatively sterile conditions, is no more toxic to infantile rats than other tissue extracts or uncatheterized urine.

2. When sterile precautions are not observed, the mortality rate among the animals increases remarkably.

3. No toxin was observed in premenstrual or menstrual endometrium.

4. No increase in toxicity was noted when estradiol was added to the menstrual blood.

5. Animals which died after the injection of menstrual blood were found to have a bacteremia, the organisms being identical with those cultured from the original menstrual material.

6. Treatment with ether rendered the menstrual blood both sterile and atoxic.

7. Antibiotics were capable of preventing death in all experimental animals.

8. Penicillin is unable to prevent menstruation and therefore does not seem able to neutralize the substance which precipitates bleeding.

Conclusions

The existence of a specific toxin in menstrual blood has not yet been conclusively demonstrated.

I am greatly indebted to Drs. J. Gurevitch, D. Weber, and E. Hendel for carrying out the bacteriological investigations, and to Dr. R. Black and Mrs. L. Beyth for their valuable help in the animal experiments.

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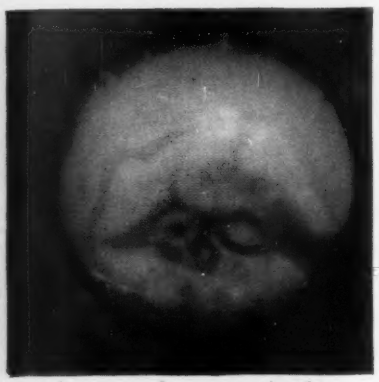
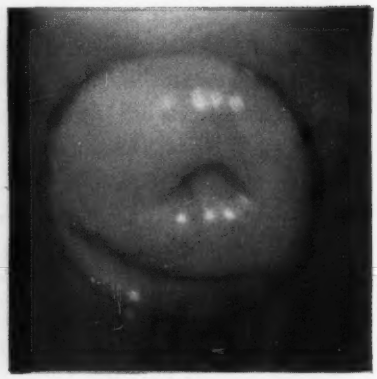
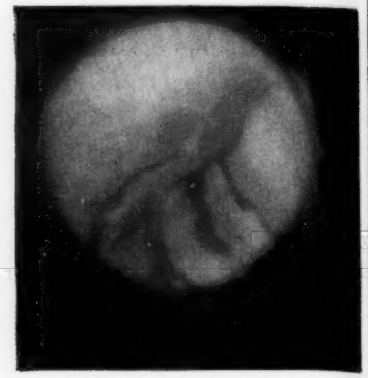


A. 1 week post-conization.

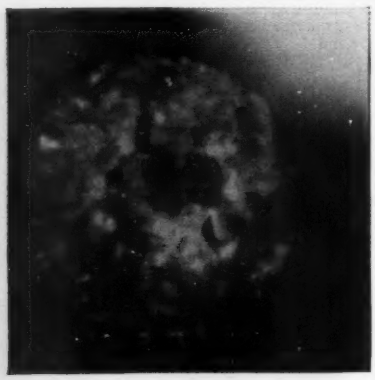


*B. 1,300 r x-ray (four pelvic ports).

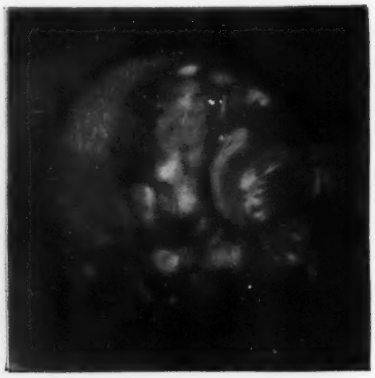


†C. 5 weeks after 6,000 mg. hr. radium.

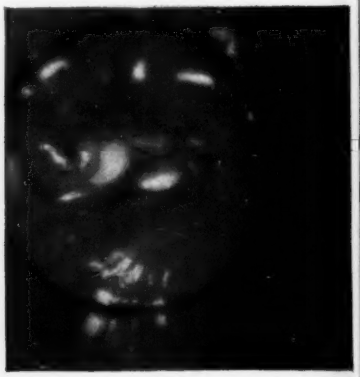
Fig. 1.—M. M., 42-year-old white para ii, gravida ii, with a history of vaginal discharge of 1 year's duration. Clinical diagnosis: erosion of the cervix. Histological diagnosis: squamous-cell carcinoma of the cervix, Grade I.



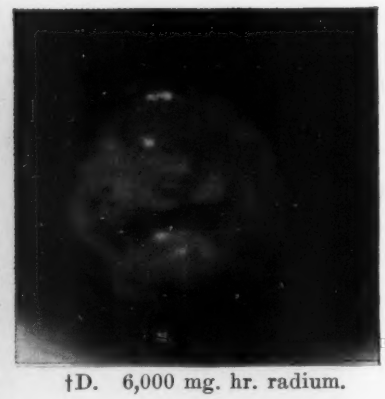
A. Prior to therapy.



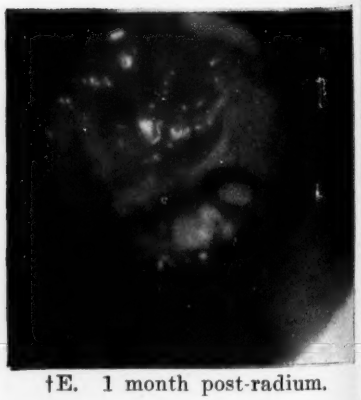
*B. 1,400 r x-ray (four pelvic ports).



*C. 2,400 r x-ray.



†D. 6,000 mg. hr. radium.



†E. 1 month post-radium.

Fig. 2.—M. A., 65-year-old white para xi, gravida xii, with vaginal bleeding of 28 days' duration. Clinical diagnosis: carcinoma of the cervix, League of Nations Stage IV. Histological diagnosis: undifferentiated squamous-cell carcinoma of the cervix, Grade IV.

*Physical factors: 260 kv., 20 Ma., 0.5 mm. Cu filter and 1.0 mm. Al filter (hvl. equivalent 0.9 mm. Cu), distance 50 cm.

†Filtration: 1.0 mm. Pt. Tandem—75 mg. radium for 3,602 mg. hr.; applicator—50 mg. for 2,400 mg. hr.

FURACIN VAGINAL SUPPOSITORIES*: THEIR USE WITH RADIATION THERAPY FOR MALIGNANT PELVIC NEOPLASMS

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VAGINAL discharge is usually a constant and most distressing accompaniment of either x-ray or radium therapy for neoplasms of the female pelvis. The discharge is persistent, malodorous, irritating, and, if unrelieved, may eventuate in polyuria, dysuria, pruritus of the vulva and vagina, and postradiation vaginal adhesions. It likewise may interfere with the curative effect of the therapeutic rays, for in the presence of infection the maximum response to a given amount of radiation cannot be obtained.[1] The vaginal discharge appears within 4 to 7 days after the initiation of radium therapy and, if not combated, gradually increases in severity and amount.

The vaginal discharge is the visual and olfactory evidence of the radiation "epithelitis," the necrosis and sloughing of the destroyed tumor tissue and the bacterial decomposition of the vaginal debris. As a result of the radiation therapy to the pelvis, there is a marked decrease in the number of the epithelial layers of the vaginal portion of the cervix and vagina. With this loss of glycogen-bearing cell layers there is a marked decrease in the availability of tissue glycogen and its ultimate conversion to lactic acid. The pH of the vagina approaches neutrality or alkalinity and the vaginal bacterial flora shifts from Grade 1 to Grade 3.[2, 3] With the growth of the secondary bacterial invaders, there is an increase in the intensity of the mucous membrane reaction with a resulting increase of tissue necrosis and slough. Depression of the secondary bacterial invaders is of primary importance in order to restore the vagina to a more normal physiological state. This bacterial depression cannot be achieved by vaginal douching alone.

The excellent results obtained with Furacin vaginal suppositories in the pre- and postoperative treatment of the cervix and vagina, as reported by the senior author, J. S.,[4] prompted the further study in the use of Furacin vaginal suppositories for the postradiation therapy of the female pelvis. Furacin (brand of nitrofurazone, New and Nonofficial Remedies) is bactericidal to the majority of bacteria found in vaginal infections. It is not bactericidal for Döderlein's bacillus (vaginal strain of *Lactobacillus acidophilus*). Its action is not seriously inhibited in the presence of such organic matter as blood, serum, and bacterial debris.

*The Furacin Vaginal Suppositories were supplied by Eaton Laboratories, Norwich, N. Y.

Furacin vaginal suppositories contain Furacin 0.2 per cent dissolved in a self-emulsifying, water-miscible base composed of glyceryl laurate 10 per cent and a synthetic water-dispersible wax 89.8 per cent. In the vagina, the suppositories melt within 10 to 15 minutes, are freely miscible with the aqueous vaginal secretions, forming a creamy emulsion which spreads uniformly over the cervix and vagina. The effectiveness of the suppository is retained for at least 6 to 8 hours.

Material

Furacin vaginal suppositories were utilized in 26 cases: 23 patients with carcinoma of the cervix, 2 patients with pelvic recurrences from adenocarcinoma of the ovary, and 1 patient with primary carcinoma of the vagina. Twenty of the cases were seen in the Tumor Clinic, Gynecological Section of Meadowbrook Hospital in the one-year period from July 1, 1951, to July 1, 1952. Six of the patients with carcinoma of the cervix were from the Gynecological Service of Fordham Hospital and have been previously reported.[4] Nineteen cases (17 patients with carcinoma of the cervix, 2 with recurrent adenocarcinoma of the ovary) were treated with deep x-ray therapy followed by intracavitary radium. Six patients with carcinoma of the cervix were treated by radium therapy. X-ray therapy alone was used for the one patient with carcinoma of the vagina. The cases and modes of therapy are outlined in Table I.

TABLE I. PATIENTS WITH MALIGNANT PELVIC NEOPLASMS FOR WHICH FURACIN VAGINAL SUPPOSITORIES WERE USED

	X-RAY AND RADIUM THERAPY		X-RAY THERAPY		RADIUM THERAPY	
	F.V.S.*	CONTROLS	F.V.S.*	CONTROLS	F.V.S.*	CONTROLS
Carcinoma of cervix	17	8			3	3
Carcinoma of vagina			1	1		
Adenocarcinoma of the ovary with pelvic recurrences	2					

*Furacin vaginal suppositories.

Routine

The following routine was initiated in all cases at the inception of radiation therapy or shortly thereafter. The patient was instructed to douche twice daily with vinegar douches (4 tablespoons of white vinegar to 2 quarts of warm water). Following the douche, a Furacin vaginal suppository was inserted into the vagina. This routine was maintained until the vaginal discharge completely disappeared.

Results

There was a marked diminution in the amount and odor of the vaginal discharge in every patient within 48 to 96 hours after the inception of this routine. In those cases when the Furacin vaginal suppositories were started just prior to or concomitantly with the radiation therapy, the patient at no time noted an odor from the scanty discharge. The individuals so treated reported a "soothing sensation" in the vagina in contrast to the rough, irritating feeling usually experienced by patients undergoing radiation therapy. The control cases treated with suppositories which contained all of the ingredients except Furacin had a minimal diminution in the character, amount, and odor

of the vaginal discharge. After a trial period on the control suppositories, these patients were placed on the Furacin vaginal suppositories with a marked decrease in the amount and odor of the discharge. The patients whose discharge was controlled by the Furacin vaginal suppositories were thereafter given the control suppositories. These patients invariably commented upon the increase in both the amount and odor of the discharge.

Untoward Reactions

One patient developed vaginal itching within 96 hours of the inception of the stated routine. This symptom promptly ceased upon discontinuance of the Furacin vaginal suppositories. Another patient developed burning and itching of the vagina, but only after having been on the medication for a period of 9 months. This symptom ceased promptly when the Furacin vaginal suppositories were discontinued.

Case Report

The following case is reported because of the unusual and excellent results obtained following x-ray therapy (Fig. 1). M. M., a 42-year-old white woman, para ii, gravida ii was seen in the Tumor Clinic of Meadowbrook Hospital on July 24, 1951, complaining of left lower quadrant pain and vaginal discharge of one year's duration. Vaginal examination revealed a marital introitus with a profuse gray discharge in the vagina. The uterus was freely movable and anterior in position. No adnexal masses were palpated. The cervix was normal in size and shape. A superficial erosion about the external os extended outward for a distance of 2 cm. A number of punch biopsy specimens were taken from the cervix. The patient was admitted to the hospital and a conization of the cervix was performed before the pathology report was received. The histological diagnosis was squamous-cell carcinoma of the cervix, Grade I. The patient was immediately placed on x-ray therapy for a total of 2,400 r to each of four pelvic ports. Speculum examination of the cervix prior to x-ray therapy revealed the central portion of the cervix to be replaced by a circumscribed area of gray necrotic slough (Fig. 1, *A*). After 1,300 r of x-ray therapy had been administered (physical factors: 260 kv.; filtration—0.5 mm. Cu, 1.0 mm. Al; distance—50 cm.) the area of slough was completely replaced by a shiny mucous membrane with no evidence of any damage (Fig. 1, *B*). Following x-ray therapy the patient received radium therapy for a total of 6,000 mg. hr. (tandem—3,600 mg. hr., applicator—2,400 mg. hr.). Five weeks after completion of radium therapy speculum examination revealed a small segment of the anterior lip of the cervix still present. The posterior lip of the cervix was flush with the vaginal vault, a small area of slough presenting at the cervicovaginal junction (Fig. 1, *C*).

Comment.—This case graphically illustrates the excellent regenerative capacity of the cervical epithelium in the absence of vaginal infection.

Summary

Furacin vaginal suppositories were utilized in 26 women undergoing x-ray or radium therapy to the pelvis for some type of malignant pelvic neoplasm, i.e., carcinoma of the cervix or vagina, and pelvic recurrences of adenocarcinoma of the ovary. The Furacin vaginal suppositories markedly decreased the amount and odor of the vaginal discharge which is usually a constant, persistent, and uncomfortable accompaniment of this type of therapy. By reducing the vaginal infection, the Furacin vaginal suppositories contributed to a better response of the malignant tissue to a given unit of radiation. In only two cases was sensitivity observed, and in one of these cases only after 9

months of almost constant therapy with the Furacin vaginal suppositories. Photographic evidence is presented illustrating the excellent response of a markedly infected and necrotic cervix to x-ray therapy.

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THE RELATIVE EFFICIENCY OF DIAGNOSTIC TECHNIQUES IN THE DETECTION OF EARLY CERVICAL CANCER*

A Comparative Study With a Survey of 1,000 Normal Women

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WITH the general acceptance of cytologic techniques and their incorporation into the gynecologic armamentarium, gynecologists concerned with diagnostic problems have sought to codify their diagnostic equipment with respect to precision and adaptability. We are faced now with the need for presenting to the general practitioner, who is in the front line of our strife for early diagnosis, a clear picture of the accuracy that he may expect from the cytologic laboratory, the relative merit of cell smear and biopsy, and the role that the clinician should play in the most efficient use of each diagnostic technique.

Such a presentation requires a disciplined appraisal of our work and an orderly survey of its accomplishments and objectives. We can teach effectively only when we understand the attainments and deficiencies of our own work. We can interpret any cytologic work significantly only if it has been carefully controlled by proper histologic and clinical studies. In an effort to make such an appraisal we have made a correlative exposition of the cytologic diagnostic work of several clinics that have evaluated and published accuracy figures, and then tried to understand these figures by a comparison with our own work whose deficiencies we can inspect at firsthand.

I. A Tabulation of Published Reports of Cytologic Accuracy

Moderate variation as evaluated by our standards is revealed by tabulations of published reports of cytologic accuracy from several of the more experienced laboratories in this country. This accuracy is based on the percentage of positive smears in patients with histologically proved malignant lesions of the cervix or endometrium, with a suspicious smear considered as a false negative unless it has been followed by a positive one. It has not been possible to apply this latter criterion to some published reports, for their authors have sometimes omitted their own accuracy standards in presentation. Obviously this is one of the factors in the variation.

In general, the reported accuracy of smear diagnosis in frank clinical cervical cancer varies from 75 per cent to 95 per cent with that of cancer in situ lying in the same general range at a slightly lower level. The smear accuracy for endometrial cancer is almost invariably lower, varying from 50 per cent to 85 per cent in those reports whose quantity permits significant analysis (Table I).

*Presented at the National Cancer Conference, March, 1952, Cincinnati, Ohio.

TABLE I. ACCURACY OF CYTOLOGIC DIAGNOSIS, UTERUS

	TOTAL PATIENTS STUDIED	SQUAMOUS CARCINOMA OF CERVIX		INTRAEPITHELIAL CARCINOMA OF CERVIX		ADENOCARCINOMA OF ENDOMETRIUM		TOTAL ACCURACY	
		NO.	PER CENT ACCURACY	NO.	PER CENT ACCURACY	NO.	PER CENT ACCURACY	NO.	PER CENT ACCURACY
Achenbach, Johnstone, and Hertig[1]	60	—	—	60	72	—	—	—	—
Isbell, Jewett, Allen and Hertig[8] Free Hospital for Women, Boston	1,000		97.5	—	—	—	83.4	—	90.45
Botsford and Tucker[2] Peter Bent Brigham Hospital, Boston	3,000	43	92.1	—	—	22	86.9	65	89.5
Burns and Hartung[3] Mercy Hospital, Toledo	6,437	54	85	—	—	20	50	74	67.5
Cuyler, Kaufman, Carter, et al.[4] Duke University Hospital	15,217	409	91.5	95	23+ 57±	44	74.6	548	63.0
Day[5] Strang Clinic, New York City	16,246	4	100	32	96.8	9	77.7	45	91.5
Gates and Warren[6] Mass. State Diagnostic Clinic	1,300	—	—	—	—	—	—	—	77
Graham and Meigs[7] Mass. General Hospital	8,131	432	90	40	87.5	—	—	472	88.2
Jones, Neustaedter and Mackenzie[9] Post-Graduate Hospital, New York City	434	—	—	—	—	—	—	—	92.1
Nieburgs and Pund[10] Georgia	10,000	106	81.1	68	82.3	4	50	178	71.1
Papanicolaou[11] New York Hospital	124	15	90	—	—	4	100	19	95
Private Patients	777	6	90.9	—	—	5	100	11	95.4
Reagan and Schmidt[12] Western Reserve	918	60	100	12	91	34	88	106	93
Reicher, Massey, and Bechtold[13] Syracuse University	3,500	67	94.1	—	—	18	72.2	85	83
Riley, Behrman, et al.[14] University Hospital, Ann Arbor	2,008	—	—	—	—	—	—	120	78
Scheffey, Rakoff, and Hoffman[15] Jefferson Hospital, Philadelphia	500	—	70.2	—	—	—	66.7	—	68.9
Sloane Hospital, New York City	1,000	31	91.1	12	80.0	17	77.2	72	87.07
This study—first 1,000 Total—this study	11,019	110	84.2	50	83.4	69	69.4	229	79

The smear accuracy of our own tumor clinic and its laboratory at the Sloane Hospital is as follows:

Squamous-cell carcinoma of cervix	84.2%
Intraepithelial carcinoma of cervix	83.4%
Corpus cancer (endometrium)	69.4%

A. The Role of the Laboratory.—

It is clear that the experience of any laboratory and its criteria for reporting accuracy are responsible for some of this variation. There is no doubt that the inclusion of suspicious but not clearly positive smears as correctly diagnosed cases will increase the reported accuracy. But it will also perpetuate the suspicion of those morphologists who have been cautious in accepting cytology as a diagnostic tool and confuse the clinician who must make a plan for treatment. This is true even if the latter is cautioned that he should never plan treatment before confirmation by biopsy. We know, for example, that inflammatory and metaplastic changes in the cervix may furnish the basis for a Class III (suspicious) cell smear.

B. The Role of the Clinician.—

Certainly the number of cell smears studied in each case, especially if more are obtained at interval examination, will affect accuracy, for dilution, quantity, and care in obtaining the material are of great importance. This is reflected in our own series where accuracy was as great in carcinoma in situ as in frankly invasive cancer; in the latter group we studied smears submitted by all members of our clinical staff on ward and private patients, whereas in the former the smear material was obtained directly, in most instances, by our own cytologic technicians. This sampling difference is noted throughout our series (Table II). With increasing experience our accuracy did not necessarily increase statistically, for we received material from more varied sources, apparently obtained indifferently at times. Furthermore, as clinicians gained confidence in our cytology laboratory, and with a coning biopsy technique available, patients with suspicious smears sometimes came to a definitive biopsy and then immediate treatment for those cases proved positive, without further smear material being submitted to the laboratory. There is no doubt that in our hands the cell study taken directly from the cervix is more efficient with respect to early cervical cancer than that aspirated from the posterior fornix.

TABLE II. ACCURACY OF VAGINAL CYTOLOGY, SLOANE HOSPITAL

	FIRST 1,000 CASES			ADDITIONAL 9,960 CASES			TOTAL CASES 10,960		
	NO. OF MALIGNANCIES			NO. OF MALIGNANCIES			NO. OF MALIGNANCIES		
	POSITIVE	NEGATIVE	PER CENT ACCURACY	POSITIVE	NEGATIVE	PER CENT ACCURACY	POSITIVE	NEGATIVE	PER CENT ACCURACY
Squamous carcinoma of cervix	31	3	91.1	60	19	77.3	91	22	84.2
Intraepithelial carcinoma of cervix	12	3	80.0	33	5	86.8	45	8	83.4
Adenocarcinoma of endometrium	17	5	77.2	32	20	61.6	49	25	69.4

The sampling discrepancy is also evident in the analysis of our own cases of adenocarcinoma of the corpus. Here we can qualify 20 errors in our second group of 52 cases (61.6 per cent accuracy) by demonstrating that 17 of these

20 false negative reports were in private cases with 12 of these smears containing no endometrial cells and 4 called Class III (suspicious). Thus in 31 private patients with corpus cancer we noted 17 errors, an inaccuracy of 54.8 per cent, but in 21 ward patients (including 1 Class III), 3 errors, or 13.4 per cent inaccuracy. We have satisfied ourselves that it is not possible to obtain proper material for diagnosing endometrial cancer by conventional cervical and fornical smears and have thus added material obtained from the upper cervical canal by pipette or cannula in patients studied in our own ward tumor clinic.

C. The Role of the Tumor.—

It is also evident that the health and site and biology of the tumor will affect the accuracy of the smear. A tumor which has not yet freely erupted on the surface may give meager exfoliation and the gross tumor with a markedly necrotic surface will also occasionally give a disappointing cytologic result. Similarly the well-differentiated adenocarcinoma of the endometrium with cell formations that the pathologist cannot call individually malignant should not be expected to exfoliate cells that are distinguishable as tumor cells on a smear; in these cases the histologist can only make his appraisal of malignancy by the over-all endometrial pattern.

TABLE III. COMPARISON OF ACCURACY OF INITIAL SMEAR AND BIOPSY

Squamous Cell Carcinoma of Cervix		79 cases
19 smear errors (of which 11 were Class III), accuracy	77.3%	
Initial biopsy accurate	93.6%	
Initial smear positive or suspicious (III)	89.8%	
5 patients with positive or suspicious (III) smear had negative initial biopsy		
Intraepithelial Carcinoma of Cervix		38 cases
5 smear errors (1 a Class III), accuracy	86.8%	
Initial biopsy accuracy	89.4%	
Initial smear accuracy (Class III, IV, or V)	89.4%	
4 patients with positive or suspicious smear had negative initial biopsy		

TABLE IV. ROLE OF CYTOLOGY IN DEFINING BORDERLINE CERVICAL LESIONS

	SYMPTOMS	INITIAL SMEAR	INITIAL BIOPSY	FINAL BIOPSY
H. A.	0	5/2/50 III 5/3/50 IV	Chronic cervicitis Possible basal-cell hyperplasia	Intraepithelial carcinoma
W. M. D.	Metrorrhagia, one episode	IV	Chronic cervicitis	Extreme basal-cell hyperplasia Intraepithelial carcinoma
C. B.	Postmenopausal bleeding	11/3/50 III 11/9/50 V	Normal cervix	Intraepithelial carcinoma
Mrs. W. S.	0	IV	Normal squamous epithelium	Extreme basal-cell hyperplasia Possible intraepithelial carcinoma
B. V.	0	IV	Squamous metaplasia	Extreme basal-cell hyperplasia Probable intraepithelial carcinoma
R. M.	0	IV	Chronic cervicitis Basal-cell hyperplasia	Extreme basal-cell hyperplasia Probable intraepithelial carcinoma
L. B.	0	5/15/51 IV 12/28/51 II	Extreme basal-cell hyperplasia Possible intraepithelial carcinoma	Mild basal-cell hyperplasia

II. Comparison of Accuracy of Initial Smear and Biopsy

Evidence to support the initial scouting opportunity of the smear in relation to the initial biopsy in our series is given in Table III.

It is important to note that many of these patients were asymptomatic and would never have come to biopsy if the smear had not indicated it. It is also our belief that our use of the coning circumferential biopsy was responsible for the high degree of accuracy of the initial biopsy in these early or seedling lesions.

Basal-cell Hyperplasia, 40 cases.—

This diagnosis is always made by biopsy material, of course. Of these 40 patients, 17 had suspicious or positive smears.

In this group fall a small but significant number of patients with biopsies showing marked basal-cell hyperplasia extensive enough to suggest possible intraepithelial carcinoma. Without serial sections it may be difficult to know whether the malignant change comes to the surface, completing the malignant quality of the entire mucosa. A positive smear may indicate that exfoliation of malignant cells is taking place; therefore, one must assume completion of the change throughout all layers of the epithelium in such cases (Table IV).

III. A Study of Early Detection: Comparative Studies of Smear and Coning Biopsy in 1,000 Normal Women Over 35 Years of Age

These patients were studied in the Columbia-Presbyterian Medical Center Group Diagnostic Clinic where medical and surgical patients of all types are referred for diagnostic work-up. This study was set up to appraise the value of our diagnostic techniques in the detection of cervical cancer in gynecologically asymptomatic women.

These patients were carefully interviewed to be certain that their history contained no symptoms suspicious of cervical cancer. A pelvic examination was performed to rule out signs suggesting cervical cancer.

Cervical and vaginal (fornix) smears were obtained by our own cytologic technicians and a coning biopsy (endocervical coning biopsy curette) was taken by a member of our Sloane Hospital resident staff. In the pathology laboratory multiple sections (usually 6) were taken from each block in an effort to strike the squamocolumnar junction at intervals.

The results of this study are shown in Table V.

TABLE V. STUDY OF 1,000 GYNECOLOGICALLY NORMAL WOMEN OVER 35 YEARS OF AGE

Intraepithelial Cancer of Cervix		16 or 1.6%
In 9 there were actual or questionable tongues of early invasion		
Smears positive	12	
Suspicious (Class III)	2	
Negative	2	
Clinical Appearance:		
Normal cervix	6	
Chronic cervicitis	5	
Erosion	5	
Basal-cell Hyperplasia		18 or 1.8%
Smears positive	2	
Suspicious (Class III)	7	
Negative	9	
Clinical Appearance:		
Normal cervix	13	
Chronic cervicitis	1	
Erosion	3	
Hypertrophy	1	

TABLE VI. ENDOCERVICAL CONING BIOPSY—TOTAL SCREENED GROUP, 1,000 PATIENTS—ASYMPTOMATIC INTRAEPITHELIAL CARCINOMA OF THE CERVIX 16, OR 1.6 PER CENT

PATIENT	AGE (YEARS)	SYMPTOMS		CLINICAL DIAGNOSIS		ENDOCERVICAL CONING BIOPSY	SMEAR
		GENERAL	PELVIC	GENERAL	PELVIC		
C. P.	37	Abdominal and leg pain	Dysmenorrhea	0	Fibromyomas of the uterus and cervical erosion	Intraepithelial and early invasive carcinoma of cervix	IV
I. G.	38	Lump in groin	0	Femoral hernia	0	Intraepithelial and early invasive carcinoma of cervix	IV
B. H.	58	0	0	0	Chronic cervicitis	Intraepithelial carcinoma of cervix	V
A. S.	65	Rectal pain	0	Conversion hysteria	0	Intraepithelial and early invasive carcinoma of cervix	IV
C. A.	34	Right lower quadrant pain	Right lower quadrant pain	0	Fibromyomas of the uterus, chronic salpingitis, and chronic cervicitis	Intraepithelial carcinoma of cervix	V
V. B.	39	0	Abdominal pain	0	Chronic salpingitis and cervical erosion	Intraepithelial carcinoma of cervix	IV
M. A.	41	Anginal pain	0	Congenital heart disease	Cervical erosion. No gynecologic disease	Intraepithelial and early invasive carcinoma of cervix	V
J. B.	36	Choking sensation in throat	0	Hysteria. Possible duodenal ulcer	Cervical erosion. No gynecologic disease	Intraepithelial carcinoma of cervix	II
R. C.	41	Palpitations, lump in neck	0	Toxic goiter	No gynecologic disease	Intraepithelial and early invasive carcinoma of cervix	IV
T. H.	46	Pain in left wrist	Stress incontinence of urine	0	Cystocele. Rectocele. Normal cervix	Intraepithelial carcinoma of cervix	V
A. W.	33	0	0	0	Chronic salpingitis. Cervical erosion. Fibromyomas of the uterus	Early invasive squamous-cell carcinoma of cervix	V
R. B.	35	Bleeding from rectum	0	? Gastrointestinal pathology. Functional disturbance	Retroverted uterus with chronic cervicitis	Early invasive squamous-cell carcinoma of cervix	III
M. V.	51	Epigastric pain	0	Obsessive fixation on gall bladder	Second degree retroversion	Intraepithelial carcinoma of cervix	II
C. L.	47	Abdominal cramps, constipation, and diarrhea	? 1 episode of menorrhagia 0	No organic disease; menopause; anxiety state	Cervicitis	Early invasive squamous-cell carcinoma of cervix	III
H. A.	40	0	0	0	Bartholin cyst	Intraepithelial carcinoma of cervix	III IV
M. H.	39	0	0	0	Chronic cervicitis	Intraepithelial carcinoma of cervix with possible invasion	V

TABLE VII. ENDOCERVICAL CONING BIOPSY—TOTAL GROUP SCREENED, 1,000 PATIENTS—SUSPICIOUS CERVICAL LESIONS DETECTED IN 18, OR 1.8 PER CENT

invasion

TABLE VII. ENDOCERVICAL CONING BIOPSY—TOTAL GROUP SCREENED, 1,000 PATIENTS—SUSPICIOUS CERVICAL LESIONS DETECTED IN 18, OR 1.8 PER CENT

PATIENT	AGE (YEARS)	SYMPTOMS		DIAGNOSIS		ENDOCERVICAL CONING BIOPSY	SMEAR
		GENERAL	PELVIC	GENERAL	PELVIC		
D. F.	34	Paresthesia, fingers	0	Raynaud's disease	0	Basal-cell hyperplasia of cervix	III
L. A.	50	0	0	0	0	Basal-cell hyperplasia of cervix	III
S. C.	33	Lump in groin	0	Fibroma, canal of Nuck	Fibromyomas	Basal-cell hyperplasia of cervix	III
J. O.	25	Indigestion	0	No organic disease	0	Basal-cell hyperplasia of cervix	IV
R. P.	42	Low back pain	0	Orthopedic disease	Mild chronic cervicitis	Basal-cell hyperplasia of cervix	V
R. W.	59	Constipation	0	Rheumatoid arthritis	0	Basal-cell hyperplasia of cervix	I
R. M.	38	Check-up	0	Syphilis	Fibromyomas of the uterus, hypertrophy of cervix	Basal-cell hyperplasia, extreme	III
M. R.	35	Nervousness, weight loss	0	Thyrotoxicosis	Possible chronic salpingitis	Basal-cell hyperplasia	III
L. B.	40	Frequent colds	0	Allergic rhinitis	No gynecologic disease	Basal-cell hyperplasia	I
A. B.	37	Lower abdominal pain	0	Anxiety state. Irritable colon	Cervical erosion, possible salpingitis	Basal-cell hyperplasia	III
C. P.	36	Mid-epigastric pain	Leukorrhea	? Urinary infection	0	Basal-cell hyperplasia	I
A. B.	53	Right upper quadrant pain	0	Diverticulitis	Cystocele. Rectocele	Basal-cell hyperplasia ? Intraepithelial carcinoma	I II II
M. L.	65	Protruding perineal mass	0	0	Cystocele. Rectocele, and prolapse. Cervix normal	Basal-cell hyperplasia	II II
C. R.	54	Right upper quadrant cramps, nausea, and vomiting	Occasional watery yellow discharge	Duodenal ulcer. Xanthoma of right hip	Atrophic cervix with erosion	Basal-cell hyperplasia	II
R. W.	48	Hypertension, pain in hip, nausea	0	Hypertension, chronic cholecystitis, and cholelithiasis. Tertiary lues	Cystocele	Basal-cell hyperplasia	III II
E. D.	59	Epigastric and abdominal pain with flatus	0	Pulmonary emphysema, scoliosis, and osteoporosis of bones	Atrophic cervix	Basal-cell hyperplasia	I-O
F. B.	57	Pain in left arm and jaw	0	Hypertension, varicose veins, arteriosclerosis	Chronic cervicitis with erosion	Basal-cell hyperplasia	I
A. R.	54	Syncope	0	Chronic ulcerative colitis	? Fibromyoma	Basal-cell hyperplasia	I II O

Again one must reaffirm the value of our present detection techniques in the discovery of asymptomatic seedling cancer of the cervix, and note that the accuracy of the smear was high but fell somewhat below that of coning biopsy. The incidence of this disease in asymptomatic women over 35 is striking but not inconsistent with our newer ideas concerning the developmental phases of cervical cancer (Tables VI and VII).

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THE INCIDENCE AND ANATOMICAL DISTRIBUTION OF BASAL-CELL HYPERACTIVITY AND ITS RELATIONSHIP TO CARCINOMA OF THE CERVIX UTERI

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RECENTLY interest has centered on certain atypical changes found in the epithelium of the cervix uteri. This altered epithelium has been designated "basal-cell hyperactivity or hyperplasia" by Galvin and Te Linde.[1] It is referred to as such since there appears to be multiplication and extension upward of the basal cells which normally occupy only a single layer on the basement membrane. They show not only loss of polarity but there is cytoplasmic-nuclear disproportion with the nuclei appearing hyperchromic and showing variations in size and shape. As a rule, mitoses are rare or absent. The epithelium above this lesion appears normal. Basal-cell hyperactivity can involve not only the basal portion but the entire thickness of the epithelium, making it difficult at times to distinguish this lesion from intraepithelial carcinoma. When these changes extend beyond the midportion of the epithelium, the lesion is classified by Younge, Hertig and Armstrong[2] as anaplasia and they subdivide it further into possible, questionable, and probable carcinoma in situ. They consider these to be examples of increasingly advanced gradations of basal-cell hyperactivity. For the purpose of simplicity, however, all such epithelial changes short of intraepithelial carcinoma will be referred to in this study as basal-cell hyperactivity or hyperplasia.

It has long been a common experience for pathologists to observe anaplastic epithelium on the periphery of squamous carcinoma of the cervix uteri. This anaplasia has also been observed in an otherwise normal cervix. Schottlaender[3] believed these atypical changes were precancerous in nature. However, another school of thought felt that these changes were benign, the result of some unknown stimulus. Until recently, this abnormal epithelium has received only casual notice. The active contemporary investigation of intraepithelial carcinoma has brought in its wake an increasing interest in this anaplastic epithelium, so that efforts are being made to interpret its exact nature. Younge, Hertig, Armstrong, and Galvin and Te Linde have so frequently observed basal-cell hyperactivity merge into carcinoma histologically that they now regard its presence as a warning and feel that perhaps the lesion in some instances may be capable of progressing to intraepithelial carcinoma.

Because of this alleged relationship with carcinoma and because of the similarity in appearance of the two lesions, it seemed pertinent to investigate the incidence and anatomical distribution of basal-cell hyperactivity and, if possible, to determine whether or not any relationship existed between this

lesion and carcinoma. Although the incidence of basal-cell hyperactivity has not been previously investigated in the nonpregnant cervix, Epperson and associates[4] followed 286 obstetrical patients, obtaining biopsies during pregnancy, at delivery, and during the postpartum course. Changes in the cervical epithelium interpreted as basal-cell hyperactivity were found in 14.7 per cent of all prenatal biopsies. There was a fall in incidence of the lesion to 6.3 per cent in the postpartum period. All gradations of basal-cell hyperactivity were seen.

Materials and Methods

Four hundred nineteen total cervices were examined in the Department of Pathology at Garfield Memorial Hospital during the period beginning Nov. 1, 1950, and ending Oct. 31, 1951. Three hundred sixty-nine of these were surgical specimens and 50 were from autopsied cases. Three hundred fifty-five of the surgical specimens were totally resected uteri and 14 consisted of cervical stumps.

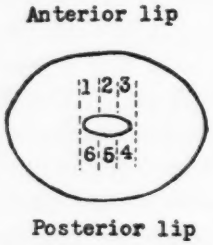

Fig. 1.—Diagram for sectioning cervix.

When the specimens were received in the laboratory, cervical smears were obtained by means of a wooden spatula, after which a routine section was cut. All smears were read before the paraffin sections were completed, and the findings were interpreted according to Papanicolaou's classification. The cervices were fixed for forty-eight hours in 10 per cent formalin, sectioned into blocks, and numbered as illustrated (Fig. 1). A minimum of six sections was cut from each cervix, additional sections being prepared in the cases showing abnormalities. All sections were studied to determine the incidence, location, and variations in appearance of basal-cell hyperactivity.

Results

The average age of the surgical patients was 41.9 years and that of the autopsied cases was 58.0 years. One hundred twenty-seven, or 32.8 per cent, of the surgical patients were Negroes. There were 18 cases of carcinoma of the cervix in this series. Twelve were invasive, 5 of which were autopsy cases. The remaining 6, or 1.4 per cent, were intraepithelial carcinoma and all were from the surgical material.

Atypical epithelium designated as basal-cell hyperactivity was present in 13 cervices, or 3.1 per cent of the total number of specimens examined, with 12 coming from the surgical material and 1 from the autopsy material. For comparative purposes, the cervices showing basal-cell hyperactivity were divided into three groups. Group I included the cervices showing only basal-cell hyperactivity, Group II those cervices showing basal-cell hyperactivity plus intraepithelial carcinoma, and Group III the cervices showing basal-cell hyperactivity and invasive carcinoma. Those cervices of Groups I and II were totally em-

bedded and from 20 to 30 sections prepared from each in an effort to eliminate the possibility of concurrent carcinoma.

Group I included 6 patients with an average age of 43.3 years. The youngest was 24 and the oldest 63 years. Four were parous, with the history being unobtainable in 1 case. Five cervices were from the surgical material and 1 was from the autopsy material. Anatomically the distribution of basal-cell hyperactivity in these 6 cases was as follows: One cervix revealed the lesion evenly distributed around the external os, almost completely replacing the normal epithelium. The squamocolumnar junction was involved in all levels. Basal-cell hyperactivity was more widespread in this cervix than in the others. The epithelium was reduced in thickness. This cervix was from a woman who died of a nongynecological illness.

In 3 cases basal-cell hyperactivity was noted in all levels but one, level No. 1 failing to show the changes in each case. One case showed basal-cell hyperactivity on the anterior lip in level No. 3 only, while foci of basal-cell hyperactivity appeared in all levels of the posterior lip. The remaining cervix in this group showed areas of basal-cell hyperactivity in levels Nos. 1 and 3. Thus the lesion was widespread around the os and tended to be distributed fairly uniformly. Histologically all gradations of basal-cell hyperactivity were present in this group. Three cervices contained foci in which all but the most superficial layers of the epithelium were involved. The remaining epithelium in these and the other 3 cervices in the group exhibited multiple foci of basal-cell hyperactivity extending upward to include one-third to one-half of the epithelium. Mitoses were rare and were limited to the lower portions of the epithelium. Only 1 cervix showed any degree of submucosal inflammatory reaction.

Group II included the 4 cervices showing basal-cell hyperactivity and intraepithelial carcinoma. Although 6 cases of in situ carcinoma were noted in this study, only 4 cervices showed the two lesions to be present together. The average age of the patients in this group was 39.5 years, with the ages ranging from 30 to 60. All were parous and all specimens were from the surgical material. One cervix showed basal-cell hyperactivity in all six levels, while the 3 remaining cervices contained three foci each. The squamocolumnar junction was involved by basal-cell hyperactivity and in situ carcinoma on the anterior and posterior lips in 3 of the 4 cases. In the 1 cervix without involvement of the junctional epithelium, both basal-cell hyperactivity and in situ carcinoma were apparent only a short distance from the squamocolumnar margin. In the 4 cervices of this group, progressive gradations of basal-cell hyperactivity were present, the most marked degree involving all but the most superficial layer of the epithelial cells. The 2 remaining cases of carcinoma in situ encountered in this study failed to exhibit any areas of basal-cell hyperactivity.

Group III included the 3 cervices that showed basal-cell hyperactivity in addition to carcinoma. A total of 12 cases of invasive carcinoma, or 2 per cent, was encountered in this study. Eight were from the surgical material and 4 were from the autopsy material. The ages of the patients ranged from 51 to 72 years, with an average of 61.3 years. All of these patients were parous. The three cervices in this group were surgical specimens. Basal-cell hyperactivity in these specimens extended through two-thirds of the thickness of the epithelium and was present at the squamocolumnar junction of each cervix. The foci of hyperactivity were distributed equally over the anterior and posterior lips. It was not possible to detect any histological differences between basal-cell hyperactivity in these cervices with invasive carcinoma and the areas of basal-cell hyperactivity in the benign cervices. The foci of basal-cell hyperactivity appeared on the periphery of the areas of carcinoma, and in each case blended gradually into the tumor.

The cervical smears in Group I were interpreted as negative, Papanicolaou Class I or II. Results of the smears in Group II were as follows: one was positive, Papanicolaou Class IV, and three cases were classed as suspicious, Class III. All of the cervices in Group III gave smears which were read as positive, Class V.

Fig. 2.

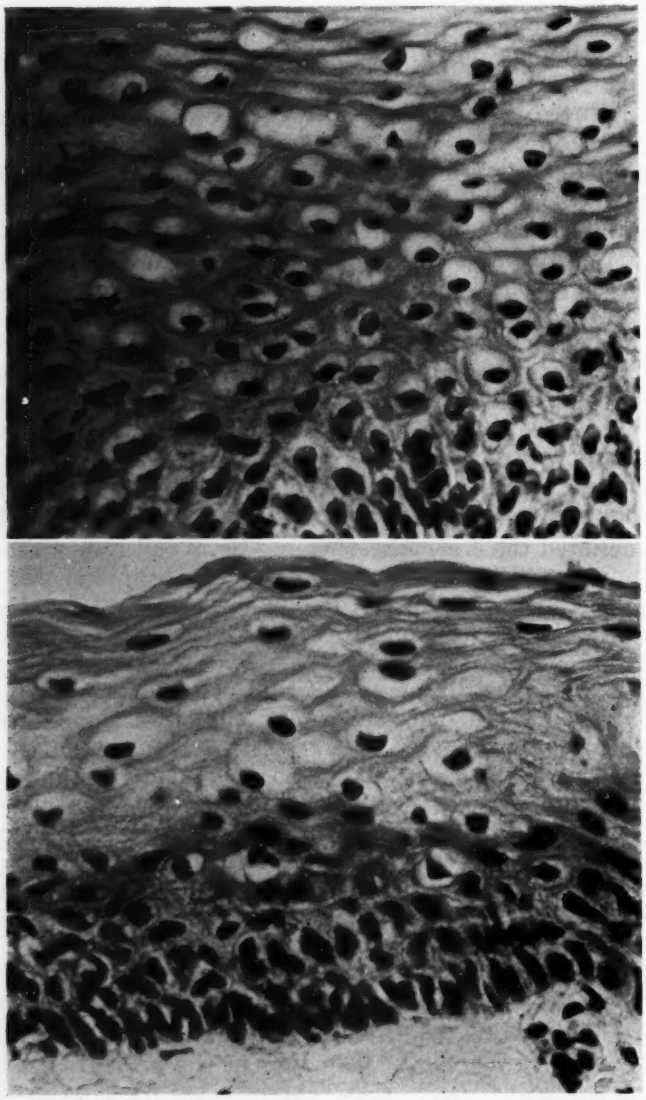

Fig. 3.

Fig. 2.—Basal-cell hyperactivity in the basal portion of the epithelium in a normal cervix. (H. and E. stain. ×885.)

Fig. 3.—Basal-cell hyperactivity involving half the thickness of the epithelium from a cervix with carcinoma in situ. (H. and E. stain. ×885.)

Comment

Thirteen cases, or 3.1 per cent of the 419 total cervices examined, showed basal-cell hyperactivity. Although this series is not large enough to be considered statistically significant, certain observations are of interest.

The average age of patients showing only basal-cell hyperactivity was 43.3 years, while the patients with both basal-cell hyperactivity and intraepithelial carcinoma had an average age of 39.5 years. The group whose cervices contained basal-cell hyperactivity in addition to invasive carcinoma averaged 61.3 years of age. Almost without exception the patients with basal-cell hyperactivity were

Fig. 4.

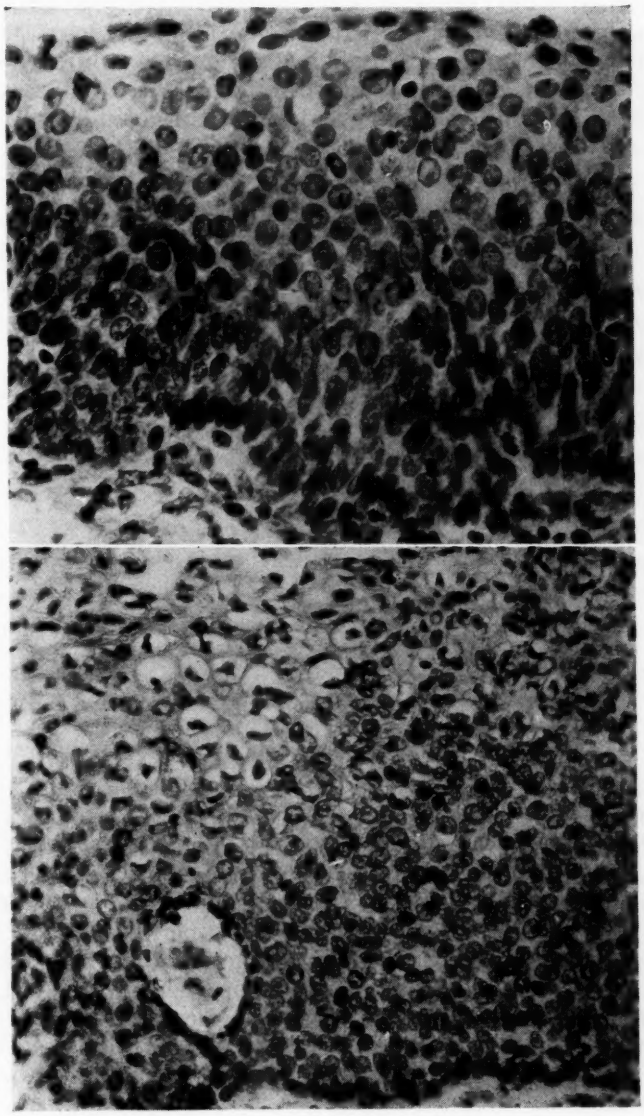

Fig. 5.

Fig. 4.—Basal-cell hyperactivity involving entire thickness of the epithelium in a normal cervix. (H. and E. stain. ×885.)

Fig. 5.—Basal-cell hyperactivity involving entire thickness of the epithelium from a cervix with invasive carcinoma. (H. and E. stain. ×750.)

parous. Histories obtained from these patients revealed no symptoms which could be correlated with the lesion, nor did gross examination of the cervix give any indication of the presence of basal-cell hyperactivity. There was no ap-

parent relationship between basal-cell hyperactivity and acute or chronic cervicitis.

Very little investigation has been done regarding the anatomical distribution of basal-cell hyperactivity. The information for this study was derived in a manner similar to the one used by Foote and Stewart[5] to determine the anatomical distribution of intraepithelial carcinoma of the cervix. Basal-cell hyperactivity displayed a definite tendency to occupy the region of the squamocolumnar junction. The junction was involved in every case but not at all levels. It was observed in all three groups that basal-cell hyperactivity was seen more frequently as the squamocolumnar junction was approached, with the lesion becoming infrequent as the distance from the os increased. Basal-cell hyperactivity was distributed fairly evenly around the os. Thus, in its anatomical

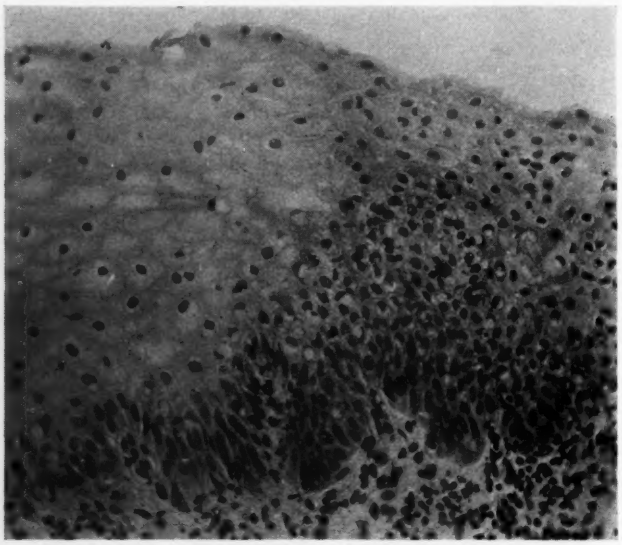

Fig. 6.—Abrupt junction between normal epithelium of the cervix and epithelium showing basal-cell hyperactivity. (H. and E. stain. ×600.)

distribution basal-cell hyperactivity mimics early carcinoma. Normal cervices as well as cervices with carcinoma disclosed all stages of basal-cell hyperactivity. Some showed involvement only of the basal portion of the epithelium (Figs. 2 and 3) while in other cervices the lesion had altered the epithelium throughout its entire thickness except perhaps for the most superficial layer (Figs. 4 and 5). The histological picture of basal-cell hyperactivity in a normal cervix was identical with that of basal-cell hyperactivity in a cervix involved by carcinoma. Frequently, basal-cell hyperactivity blended imperceptibly into intraepithelial and invasive carcinoma in the same way that intraepithelial carcinoma merges with invasive carcinoma. Galvin and Te Linde have observed basal-cell hyperactivity blend into in situ carcinoma so frequently that they have become "deeply concerned about its signficance." When they encounter basal-cell hyperactivity clinically they feel that multiple biopsies must be taken until carcinoma can be ruled out. If basal-cell hyperactivity is related to carcinoma, how can the difference in incidence be explained. The incidence of carcinoma of the cervix varies from group to group depending somewhat on the selection of material. Values have been reported varying from less than 1 per cent[6, 7] to 3.9 per cent[8] for intraepithelial carcinoma. Meigs[9] records the incidence of invasive carcinoma as 1.6 per cent in a general hospital. With one exception,

these reports reveal the incidence of both intraepithelial and invasive carcinoma to be less than 3.1 per cent, which was the incidence of basal-cell hyperactivity in this series. It is possible that basal-cell hyperactivity is a reversible lesion. It is also conceivable that basal-cell hyperactivity might advance at such a slow rate that the malignant phase is not reached during the patient's lifetime. The final answer to questions concerning the natural history of basal-cell hyperactivity and its relationship to carcinoma must await further study. And the lesion is deserving of long-term observation in order that its potentialities be accurately evaluated.

Summary and Conclusions

Four hundred nineteen cervices were examined and the lesion of basal-cell hyperactivity was found in 13 cases, or 3.1 per cent. Those cervices showing only basal-cell hyperactivity were placed in Group I, those with hyperactivity and in situ carcinoma made up Group II, while the cervices showing hyperactivity and invasive carcinoma constituted Group III. The histological variations of basal-cell hyperactivity were compared, and it was impossible to detect whether a given area of basal-cell hyperactivity came from a normal cervix or from a cervix with carcinoma. The areas of hyperactivity were distributed fairly evenly around the anterior and posterior lips. The lesion showed a definite preference for the squamocolumnar junction of the internal os. In those cervices containing tumor, there was a marked tendency for basal-cell hyperactivity to be present on the periphery of the areas of carcinoma. The basal-cell hyperactivity frequently blended imperceptibly into the areas of carcinoma.

Although the group of cervices in this series is not large enough to be statistically significant, basal-cell hyperactivity, because of its intimate relationship with carcinoma, warrants extended study.

I wish to express appreciation to Dr. Theodore Winship for his valuable suggestions in the preparation of this paper.

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SMALL PREULCERATIVE INVASIVE CARCINOMA OF THE CERVIX: THE SPRAY CARCINOMA*

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THE majority of pathologists and gynecologists believe the mechanism of the early stages of cervical carcinoma to be the following: one cell or a group of cells of the basal layer changes into carcinoma, which of the two is the right one has not yet been settled. The reason for this is that we do not know how to diagnose carcinoma by the analysis of a single cell. If carcinoma is present in a single cell of the basal layer, we probably fail to recognize it. It is more likely that a group of cells and not only a single cell changes into carcinoma, although we cannot prove it.

The changes taking place prior to this earliest phase of carcinogenesis lie more or less in the dark. Our knowledge is wider and better founded from this early phase on. It is based experimentally on the subsequent changes found in experimental skin carcinoma in the mouse following tar applications. The concept that carcinogenesis is the same in analogous epithelia of different organs and has the same mechanism of origin and spread is not justified. It may be so, but need not be. Similar organs may have different ways of developing carcinoma and the same organ in different animals may develop carcinoma in a different way.

The first step according to this concept of cervical carcinogenesis is that it starts from a short row of basal cells, which without previous morphological changes assume a carcinomatous character. Just as the normal basalis normally reproduces the higher zones and layers of the normal squamous epithelium, so do the carcinomatous cells of the basalis reproduce the upper zones of the epithelium, but with cells of carcinomatous character. The mechanism in the normal development is as follows: A basal cell undergoes mitotic division; one of the newly formed cells remains in its basal location, the other cell is forced upward without losing or destroying its connections with neighboring cells. In a similar manner, the latent carcinomatous basal cell builds a carcinomatous epithelium. The normal basal epithelium produces normal cells which by progression into higher strata undergo differentiation. However, the carcinomatous cell replacing the normal cell usually does not acquire a function or a higher differentiation. Characteristically in the first stage of cervical carcinogenesis, there can be seen cells of complete immaturity, and nuclei of atypical bizarre shape located close to the epithelial surface. The presence of large, misshaped hyperchromatic nuclei in a stratum which normally has hornified scales without nuclei supports the diagnosis of car-

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cinoma. Attributes, such as "irregular," "polymorphous," "atypical," cannot be defined so precisely that two investigators, independent of each other, will make the same diagnosis. These terms leave a wide range to individual interpretation and are also used for noncarcinomatous cells. Still more ambiguous are the intermediate gradations introduced by Hinselmann, such as "increasingly atypical." The differential diagnosis between "atypical" and "increasingly atypical" cells is often very difficult. Usually the pathologist's personal experience and the subconscious comparison with previously seen cases help decide whether the irregularity has sufficiently progressed to justify the diagnosis of carcinoma.

Among the various characteristics considered significant for diagnosis of carcinoma is one of more accurate nature which if present would permit differential diagnosis without doubt. This change is described in numerous papers and textbooks as "breaking through the basal membrane" or "breaking the basal membrane." This character deserves investigation for its disjunctive and decisive nature.

The first stumbling block encountered in such an investigation is the difficulty met in so many problems in pathology, the difficulty of terminology. This terminological difficulty is greater in gynecological pathology than in any other chapter of pathology, different authors using one and the same term in a different sense. Before going into the discussion of the breaking of the basal membrane, the term basal membrane needs clarification.

A basal membrane in the stratified epithelium of the skin has been acknowledged as present by some authors and denied by others. There are a great number of papers dealing with the presence or absence of a basal membrane in the skin. Pathologists and dermatologists have applied numerous and various methods to the investigation. The analogous question of the presence or absence of a basal membrane between the cervical stroma and the cervical squamous epithelium has been neglected. The various methods used by dermatologists and pathologists have not been applied to prove the presence or the absence of a basal membrane in the cervical surface, although the fact that erosions are frequent in the cervix and rare in the skin may possibly be due to different attachment of skin epithelium and cervical epithelium. The use of the criterion of whether the epithelium breaks through the basal membrane cannot be considered without previously settling the question of whether or not there is a basal membrane in the cervix and if so whether it is disrupted by beginning carcinoma.

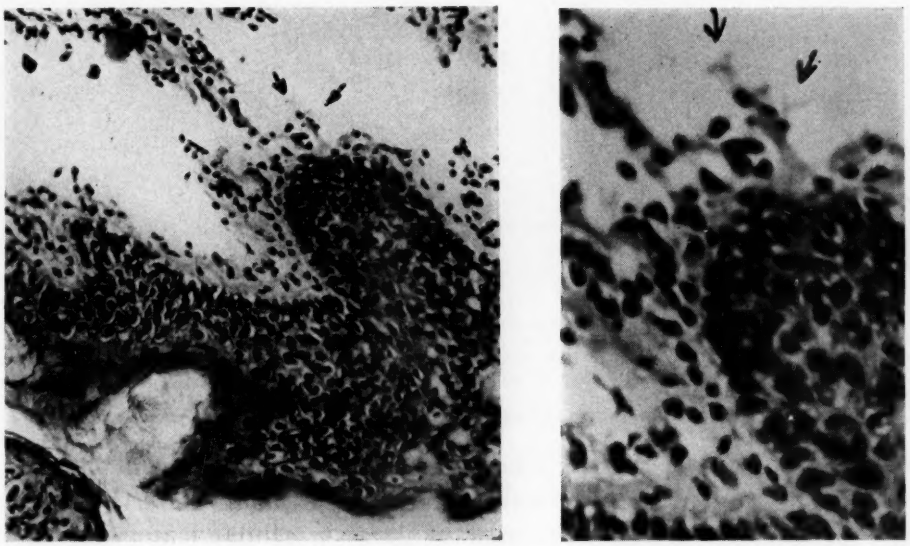
Some authors use the term basal membrane to include all of the cells of the basalis. This differs from what is called a basal membrane in other organs. The term in the latter sense signifies a firm translucid film of homogenous structure underneath the basal cells and extending in two dimensions, whereas the third dimension is small. They presume that the basal end of the cells which form the basalis of the epithelium anchors at the inner surface of a basal membrane. In this sense the term is used to describe basal membranes of the testicle, of the ear, and of the intestinal mucosa. In no organ is the term "basal membrane" used for a multitude of cells. This misnomer has led to misunderstanding and a great number of errors.

Other authors identify the term "basal membrane" with a thin film which is supposed to lie between the basal end of the basal cells and the connective tissue of the underlying stroma. Most investigators of skin histology do not believe that the skin has a basal membrane of this type, nor has a basal membrane of this type been accepted for the cervix. Thus the question remains: By which mechanism is the epithelium fixed to the subepithelial stroma? There are three possibilities: (1) fixation accomplished by elements belonging to the stroma and invading the basal part of the epithelium; (2) fibers from the epithelium entering the surface of the stroma; (3) a combination of both, epithelial fibers entering the stroma, stromatogenic fibers entering the epithelium.

The second interpretation of the term "basal membrane" as used by a great number of authors is based on the following facts: the corium has a nonspecific arrangement of connective tissue bundles and a network of argentaffine fibers. It is not demonstrable with hemalum and eosin staining or with tetrachrome combinations, but with Maresch's silver impregnation method modified by Bielschowsky. The network formed by these fibrils shows areas of condensation in which the fibrils are more numerous and the structure dense, and other areas where the fibrils are less numerous. These differences in density are normal and physiological. One area of condensation is at the junction between the basal layer of the epithelium and the upper margin of the corium. The fibers beneath this line of junction do not enter the basalis but make a "U" turn doubling back into the deeper part of the corium. The result of this is that each fiber in the border line is encountered twice, whereas it may be found only once in the general network. Thus there is given the impression of a higher density in the subepithelial zone. This layer of apparently increased density is erroneously accepted as a special structure, which it definitely is not. Szodoray, one of the latest investigators, attempted to get a clear concept of the fixation of the epithelium to the corium in the skin. By utilizing special stains on the skin of the forearm he demonstrated lattice fibrils entering the epithelium between basal cells. These fibrils end approximately midway between the lower end of the nucleus and the lower end of the protoplasm of the basal cells. Utilizing different stains, he demonstrated that the basal layer cells possess flabelliform processes attached to the surface of the corium. According to his investigation the fixation of epithelium and corium is twofold: the stroma sends out lattice fibrils which are connected with the basal cells' lower end, and the basalis forms flabelliform processes by which it is anchored to the surface of the corium. As no attempt has been made to investigate the fixation of the cervical epithelium to the stroma, we tried different stains and different dyes on the cervical epithelium, without success. It is probable that the fixation in the cervix is weaker than the fixation in the skin. This minor grade of fixation may be responsible, along with the smaller number of dovetailing papillae, for the frequent erosions of the cervical epithelium.

Histologists have known for many years that, in investigation of special structures, the teasing apart of the tissue elements gives often more accurate pictures of tissue structure than those with the distortion encountered in fix-

ation, embedding, and staining. This is true in the study of the epithelial and stromal juncture of the cervix. Teasing the tissue apart to separate junctions is a difficult task. Occasionally an artefact in a paraffin slide is helpful, as equivalent to teasing the tissue elements apart. One may see in such slides the surface squamous epithelium torn from the stroma. Both border lines, the epithelial and the stromal, are denuded, and the structural fibers connecting both tissues are freed from the surrounding epithelium. This method applied to the cervical squamous epithelium shows no free fibers but another type of attachment. This is by pseudopodium-like projections of the cytoplasm of the basal cells which bridge the gap to some of the elements of the denuded upper surface of the stroma. Some structure, probably the argentaffine fiber network, lying in the upper stromal border, is the specific element to which the pseudopodia attach. The connection between the pseudopodia and the argentaffine network is difficult to demonstrate because of technical problems. This difficulty is centered about the inability to demonstrate both the stained argentaffine fibrils and the stained pseudopodia on the same slide (Fig. 1).



A. *B.*

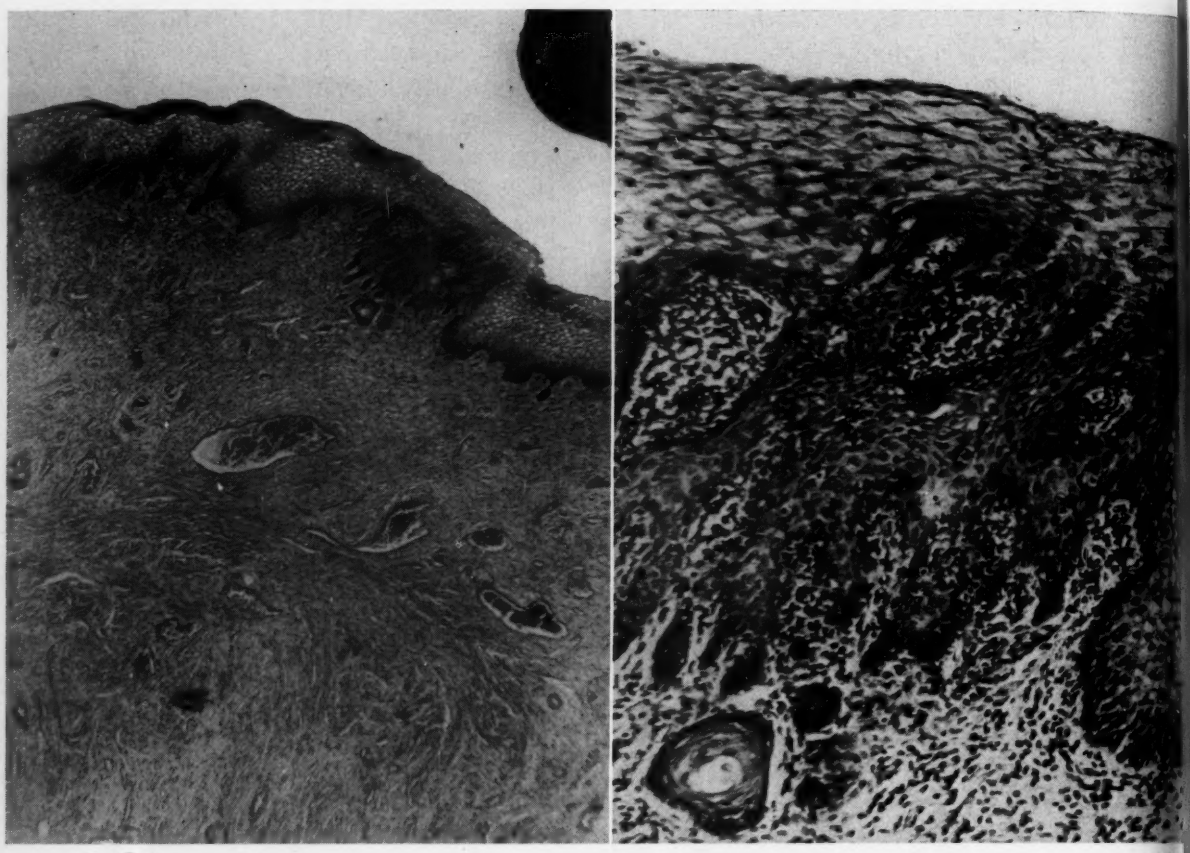
Fig. 1.—Squamous epithelium separated from stroma accidentally during fixation or embedding. There is nothing that would demonstrate a basal membrane in the strict sense of the word. Some of the basal cells show thin pseudopodia-like projections of cytoplasm. There are two cells from the basal layer of epithelium, one "A" shaped, the second "Y" shaped. Note arrows.

A, ×140.

B, ×300.

At the surface carcinoma grows by assimilation, it means transformation of the normal basal cells directly neighboring basal cells of carcinomatous character.

New problems arise if this concept of carcinogenesis at the cervical squamous epithelium, transformation on the surface and later downgrowth, is accepted. It is doubtful whether every carcinoma in the cervix develops in the same way. Virchow observed and established as fact that the progressed



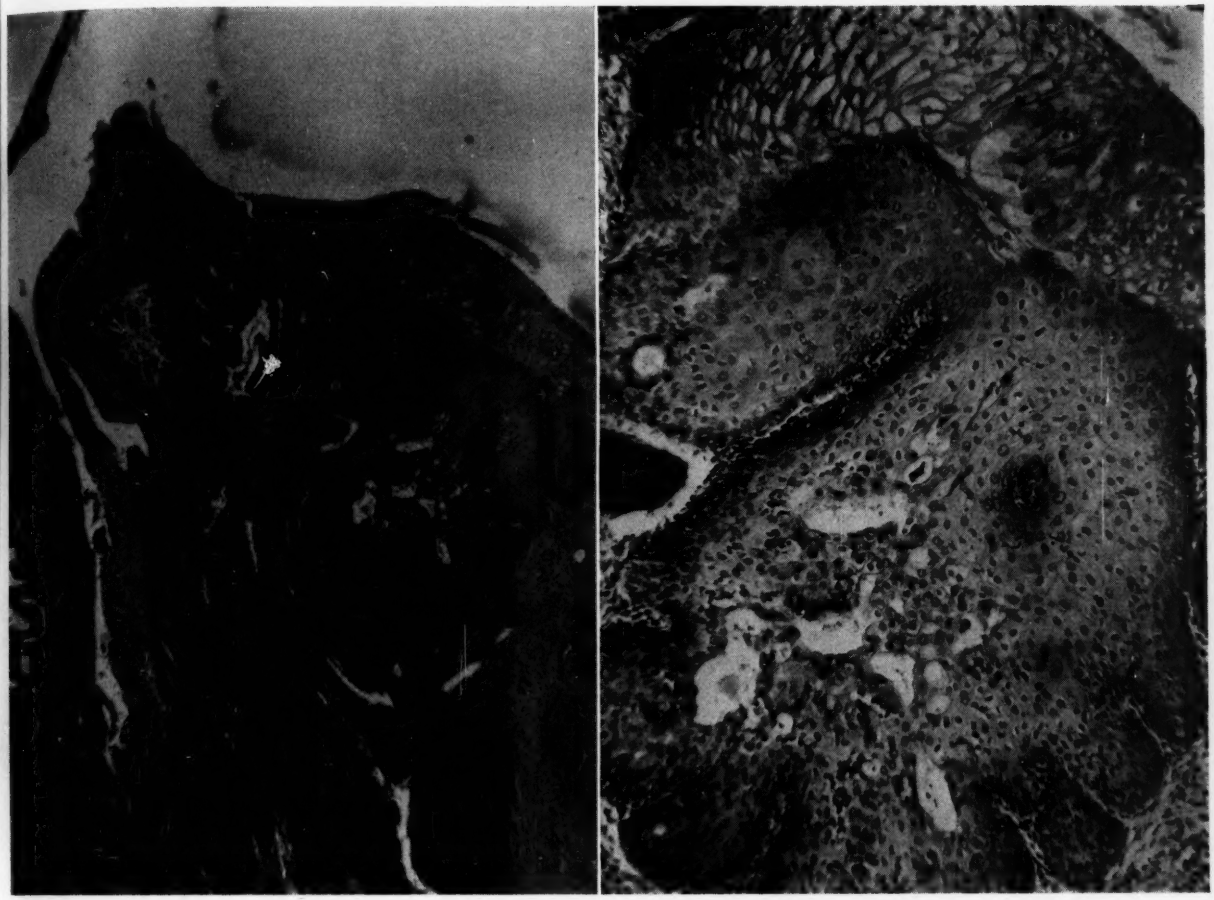
A. *B.*

Fig. 2.—M. F., aged 46 years. Extirpation of uterus and cervix for multiple fibroids.

A, Cervix, squamous surface epithelium. In a small area the basal layer transformed into an invading carcinoma of low maturity with a horn pearl as observed frequently in basal-cell carcinoma of the skin. The surface is formed of normal glycogen-containing scales which on top of the carcinoma are analogous to the surface layer on top of the normal basal-cell layer. (×45.)

B, Carcinoma and normal surface layer. (×130.)

carcinomas are different in character, both in morphology and in their behavior toward surrounding normal and invaded stroma. Here the carcinoma grows by multiplication and increase of its own cellular material. There is no more growth by transformation of neighboring cells. There is no epithelium present which by contact with downgrowing carcinoma can be transformed by assimilation. That many carcinomas originate primarily as surface carcinoma and secondarily develop by downgrowth can be admitted as proved. The question remaining is whether it is the only way of carcinogenesis of cervical carcinoma or whether still another process exists. A frequent experience in embryology is that the same end results may be achieved by two entirely different processes. As an example: granulosa cells of the ovarian follicles can develop from the primary germinal cords as well as from the secondary germinal cords. Although it has to be admitted that primary and secondary cords develop from the same celomatous matrix there is a different mechanism for the transformation of either into potential granulosa. It must be admitted that the adult ovary contains follicles with granulosa of



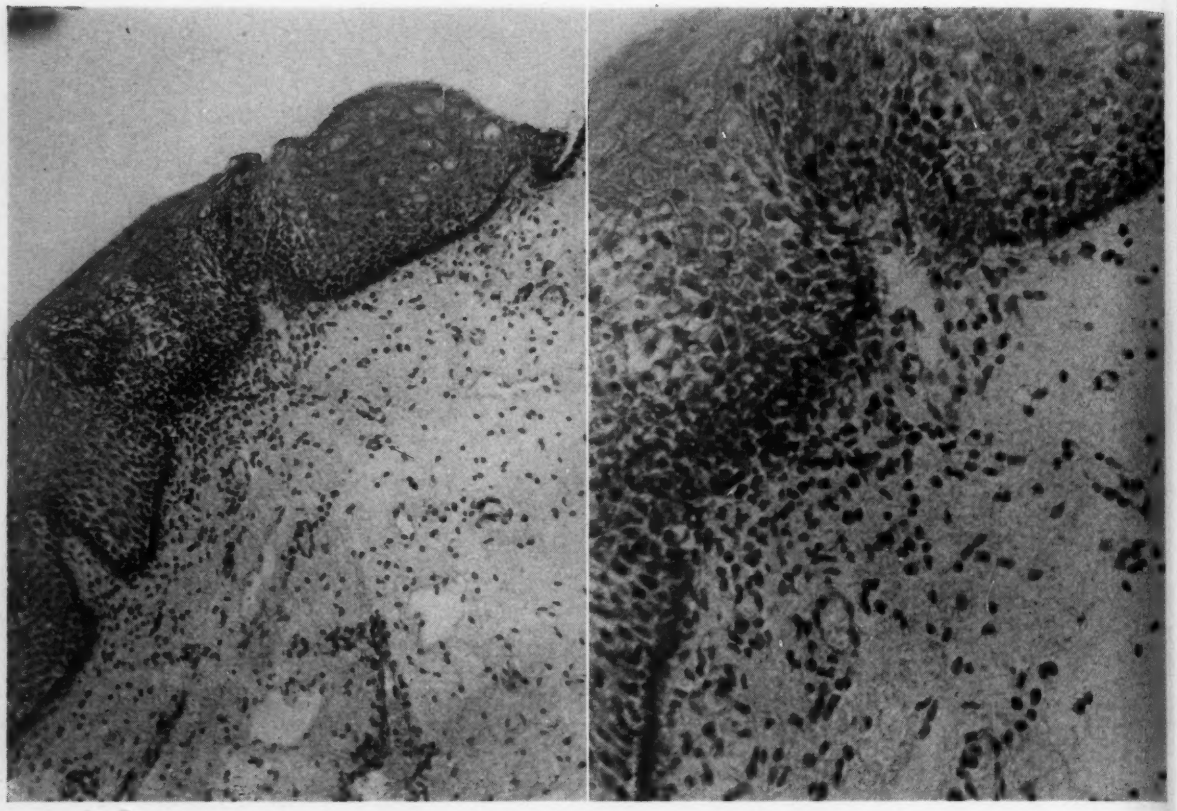
A. *B.*

Fig. 3.—M. G., aged 26 years. Extirpation of cervix for laceration.

A, The surface squamous epithelium is normal in the upper part, while the lower basal part has changed into a sharply demarcated carcinoma which invades the stroma by 3 projections. The middle projection shows 8 toelike projections as seen frequently in initial carcinomas. (×65.)

B, The same, ×100. Note the sharp demarcation line between normal and carcinomatous epithelium.

different origin: (1) from primary cords and (2) from secondary cords. However, no morphological difference or any other differentiation has been found between the two types. There is no observation that would permit differentiation of the two types of follicles either in the phase of histogenesis or in the functional changes after ovulation and transformation into a corpus luteum. Similarly, the first phases of carcinogenesis of the cervical epithelium need no be the same for all carcinomas. Two or even more different modes may exist. We have learned from a great number of cases that the interval between surface extension and downgrowth shows great variations. The interval may amount to a few weeks in some cases and to several years in others. There may be a quantitative difference but not a qualitative one. When examined histologically and clinically, there is no indication as to the length of time which it would have taken the carcinoma to develop from a mere surface carcinoma to an invading carcinoma. Comparison of cases with long and



A. *B.*

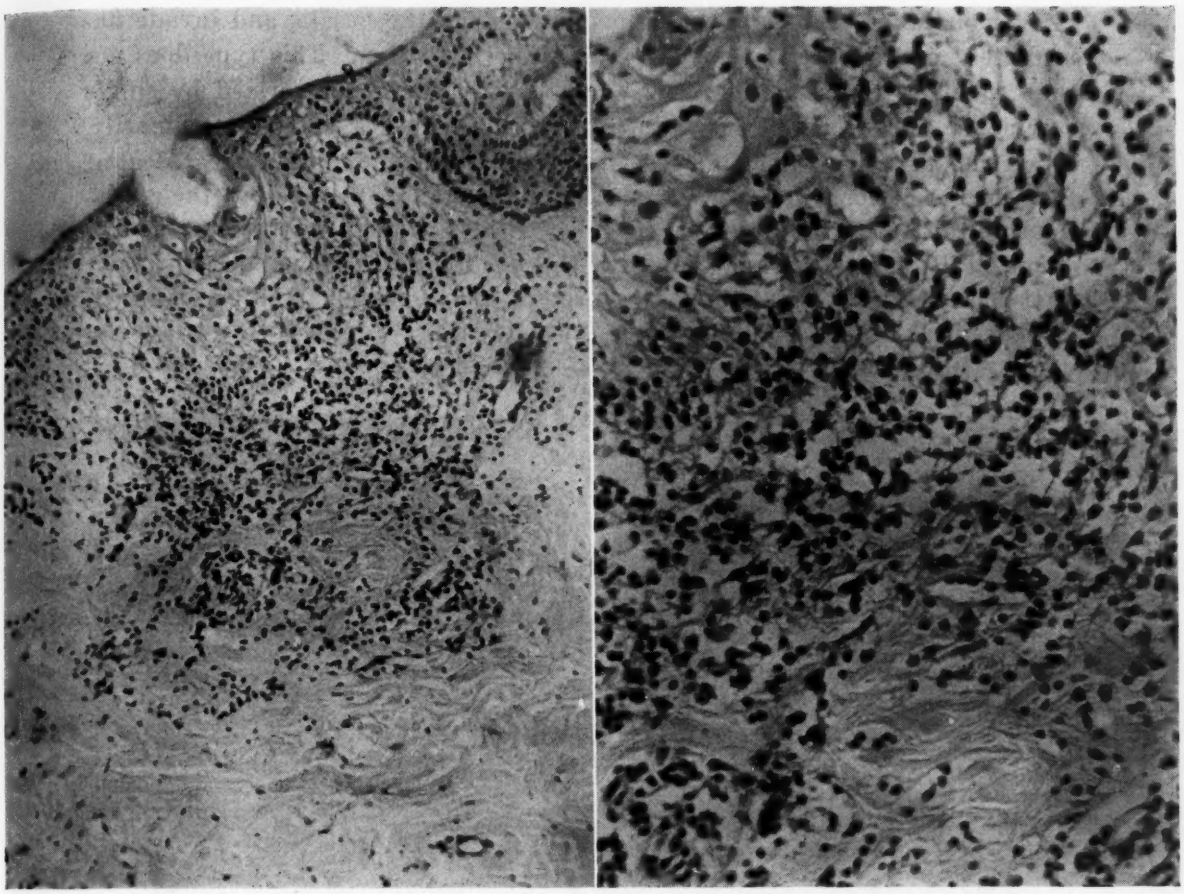
Fig. 4.—L. F., aged 23 years. Extirpation of uterus for fibroids. Cervix. Note the distinct and regular basal-cell layer in the right upper quadrant changing into carcinoma which by single cells, spraylike, invades the corium.

A, ×110.

B, ×240.

short intervals between surface carcinoma and invasive carcinoma has revealed no significant difference. This fact that cervical carcinoma has more than one way of growth and latency was pointed out, particularly by Brooke Bland. He pointed out that the surface and belated downgrowth types have been observed in many cases, but that there must be at least one more type of early developing cervical carcinoma. Whereas the surface downgrowth type is characterized by a long period of latency, he emphasized that the second type exists characterized by the speed of progress. This was a clinical observation and not supported by slides. It was just postulated. If the second type existed at all, the examination of a great number of grossly normal-appearing cases must ultimately lead to the disclosure of this type. By utilizing this method, we by chance found a few cases proving a different mode of origin and development of carcinoma. These cases are characterized by transformation of the basalis into carcinoma, immediately followed by downgrowth while the higher strata of the epithelium remain normal (Figs. 2* and 3). Carcinomatous invasion in the depth makes rapid progress. On gross inspection there is no difference shown between the area undermined by carcinoma-

*This case has been discussed from a different point of view in Arch. f. Gynäk. 155: 439, 1934, Fig. 10.



A. *B.*

Fig. 5.—B. G., aged 58 years. Carcinoma of the right mammilla (not of Padget character). Note the regular basal cells in the right upper quadrant which change into a carcinoma which invades the stroma by single cells like a spray.

This case of spray carcinoma in a duct of the mammilla proves that the spray carcinoma is not limited to the uterine cervix, but can develop from other organs as well.

A, ×110.

B, ×240.

tous basalis and the area under which normal epithelium grows. The surface gives no clue to the changes in the depth. Just as the surface carcinoma shows little difference if compared to the surface of normal epithelium on gross inspection, the carcinoma that starts by downgrowth of the basalis is not associated with specific changes of the surface. Excepted are a few cases of surface carcinoma which have the carcinomatous area a little thickened, of a purer white color, finely wrinkled and sharply demarcated from the normal epithelium. In this phase, neither the surface carcinoma nor the basal-cell downgrowth carcinoma is ulcerated. They not only present a preinvasive but also a preulcerative phase. Thus, these carcinomas of the basalis give no chance of detection by Papanicolaou stain and smear, iodine painting, or colposcopy. These cases are discovered by chance only. This fact furnishes an explanation for some of the false negative smears and stains in early carcinomas which escaped early detection.

Among the carcinomas which originate from the basalis and invade immediately is a subgroup that deserves special attention. This type does not show strands invading the stroma, but the invasion is performed by single carcinoma cells which form a brush- or spray-shaped structure. Ordinarily, in carcinoma, when the cells become carcinomatous, they lose a great deal of functional relationship to the other cells and organs, but preserve their relationship to the remaining carcinoma cells. In this particular subgroup the carcinoma cells lose all connection with the neighboring carcinoma cells, their next relatives. They lose the last residue of social relations and become freelancers of malignant character. It is probable that later on these carcinomas develop into some of those of an especially high malignancy (Figs. 4 and 5).

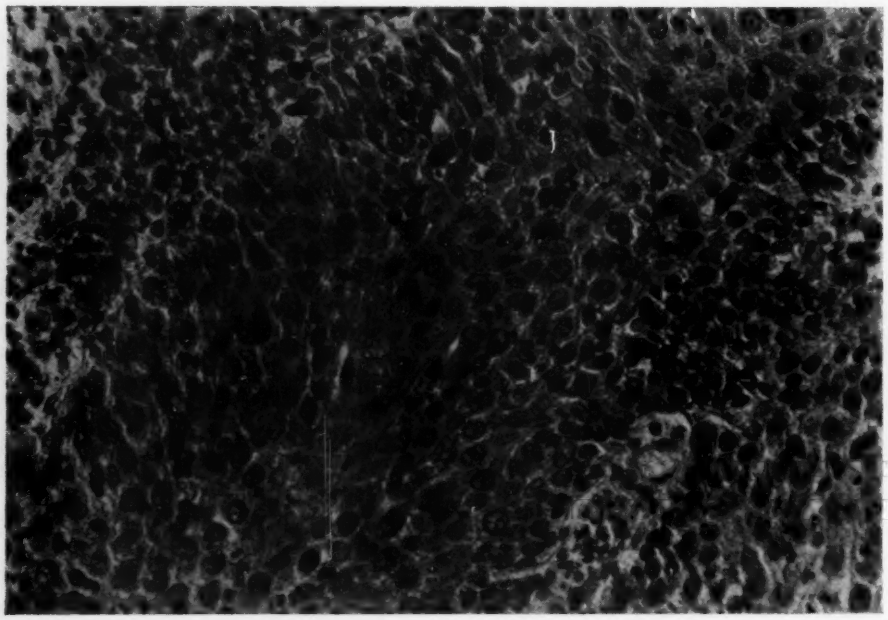
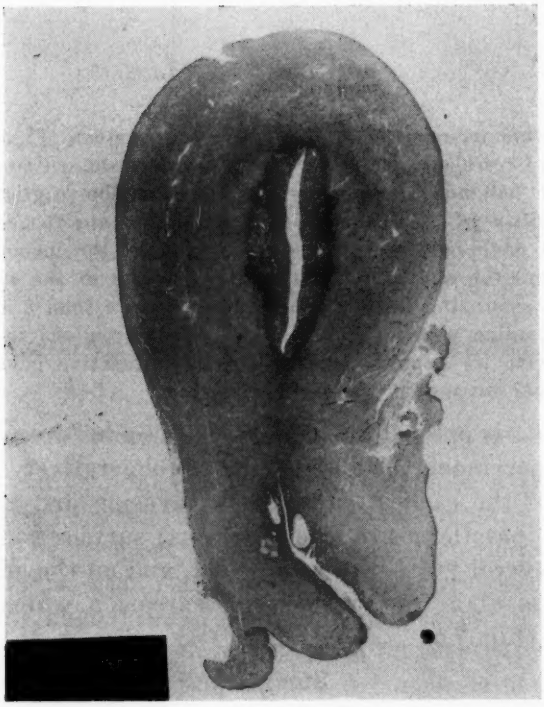


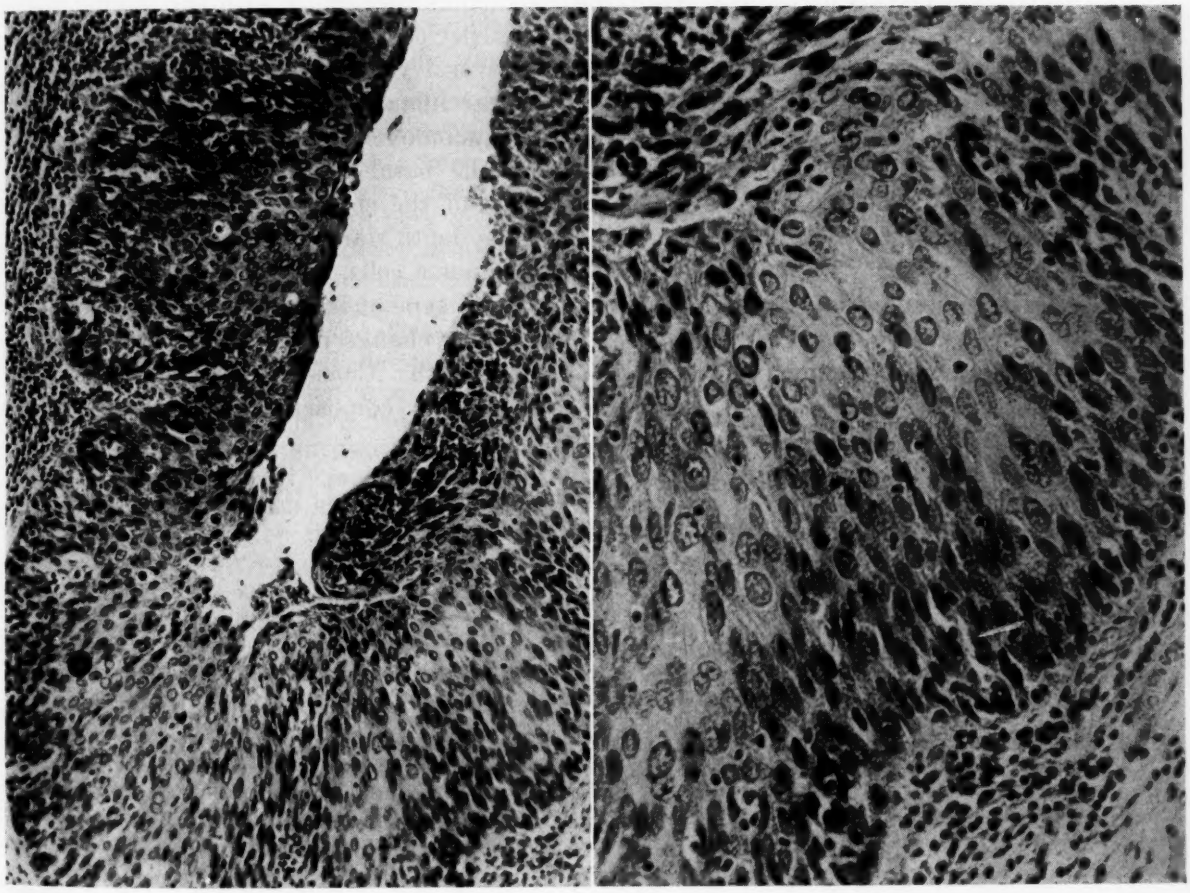
Fig. 6.—M. S., aged 31 years. Scraping after positive iodine test (white area around external os, less than 2 mm. in diameter, which remained unstained shows thin coat of surface carcinoma). (×285.)

Numerous planned observations as well as those by chance have proved that there is no fixed relationship between surface extension and downgrowth of early carcinoma. First of all, the interval between surface extension and downgrowth can vary from probably a few days to several years. No conclusion can be made from the status at the surface to the extension of the downgrowth. There may be a surface carcinoma in situ several millimeters in diameter with no downgrowth for months or years. On the other hand, a surface carcinoma of minimal size may have produced a downgrowth larger in volume than the carcinoma at the surface. The following case may serve as an example:

A patient 31 years of age came to the Clinic complaining of lumbar pain. A routine iodine test revealed an eccentric, circular white unstained area at the external os sharply demarcated from the deep brown surrounding exocervix. Parts of the white-surfaced epithelium were scraped off with sharp spoon and tissue forceps. Histologic analysis



A.



B. *C.*

Fig. 7.—M. S., aged 31 years. Uterus removed on the basis of scraping (Fig. 6).

A, The surface carcinoma which was only incompletely removed by scraping has already started downgrowth. (Marked by black ink spot.)

B, The same. (×110.)

C, The same. (×240.)

of the peeled-off epithelium revealed typical surface carcinoma (Fig. 6). Since the iodine test of the cervix had revealed a small portion of iodine-unstained tissue extending into the cervical canal which had not been removed at the time the original specimen had been obtained, the possibility of extension of the carcinoma into the cervical canal and invasion at this point could not be ruled out. In view of the incomplete removal of the surface carcinoma and the age of the patient, extirpation of the cervix and corpus was carried out. It was surprising to find a projection of more than 2 mm. in length and 0.5 mm. in diameter extending upward in the cervical canal from the carcinoma in situ. The surface carcinoma with its smooth surface in its preulcerative phase had not given the impression of its rather advanced invasive development.

This carcinoma is one of the smallest carcinomas ever operated on where the diagnosis of carcinoma had been made preoperatively. Despite the fact that this is one of the earliest carcinomas, invasion had already started. It must be realized that there are two extremes: surface carcinomas which invade only after several years of development, and on the other hand there are surface carcinomas of a few millimeters' extension which have already invaded the stroma (Fig. 7).

Summary

In the majority of cases of solid cervical carcinoma the carcinoma starts by transformation of the epithelium into a surface carcinoma with the latent prospective tendency of downgrowth. This period of latency of invasion shows great variation, from a few days to several years. There is a second mode of carcinogenesis in the cervix. The carcinomatous transformation is limited to the basal Malpighian zone of the squamous epithelium, starting invasion immediately after transformation of the basal zone into carcinoma. In such cases the upper external surface zone of the epithelium remains unchanged and normal, while the carcinoma in the depth starts invasion by downgrowth, sometimes by masses composed of carcinoma cells, sometimes by single cells developing from the basalis. For the latter type of initial carcinoma the term spray carcinoma is suggested. There is no change of the surface that would indicate carcinomatous invasion in the depth. Consequently, methods suggested for detection of surface carcinoma, as colposcopy, iodine test, Papanicolaou and Ayre smears, are of no avail.

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OVARIAN STROMAL CHANGES IN ENDOMETRIAL CANCER

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THE possibility that fundal adenocarcinoma may be a sequel to prolonged unopposed estrogen stimulation is not a recent hypothesis. Under no circumstance should it be accepted as an established fact; indeed, experimentally no laboratory animal has been made to develop true irrevocable adenocarcinoma of the fundus despite huge doses of estrogenic substances. This may be at least partially due to the unfortunate development of an aseptic pyometra in animals so treated, but the fact remains that fundal carcinoma is not produced.

Nevertheless, many recent publications have stressed the possibility that endometrial carcinoma may in some way be related to excessive protracted amounts of estrogen. This problem has been studied from a number of different angles which may be briefly summarized as follows:

1. Hyperplasia and adenocarcinoma have been observed to coexist rather frequently by such excellent gynecological pathologists as H. C. Taylor, Jr.,[1] Novak and Yui,[2] and others. All gradations from a simple hyperplasia through more proliferative forms to frank adenocarcinoma may be found in the same case, particularly by a discriminating though unprejudiced pathologist.

2. The high incidence of hyperplasia and/or adenocarcinoma (15 to 20 per cent in most series) in association with the estrogen-producing granulosa-theca-cell tumors of the ovary has been commented on by Ingraham and asociates,[3] Mussey, Dockerty, and Masson,[4] Novak and Ingram,[5] etc. This has been considered the so-called spontaneous biological experiment.

3. Many women who develop adenocarcinoma of the fundus in the postmenopausal era have had a previous curettage showing hyperplasia and/or a history strongly suggesting previous unopposed estrogen stimulation. Gusberg,[6] Randall,[7] Speert,[8] and others have noted this, and the first two state that a woman with such an atypical bleeding history has a three and one-half greater chance of later developing adenocarcinoma. Jones and Brewer,[9] however, question this presumptive evidence of the necessity of unopposed estrogen, by reporting a small series of patients, obviously premenopausal, who show either secretory endometrium or a corpus luteum (Figs. 1 and 2).

4. A disproportionately large number of women having a late menopause with resultant prolonged and often unopposed estrogen stimulation subsequently develop adenocarcinoma. Gusberg states that the menopause is most frequent between 52 and 54 years in his series. Thirty-five per cent of Randall's patients with adenocarcinoma had their menopause over the age of 50. Other authors such as Henriksen,[32] and Marshall[31] feel that the menopause is not delayed.

5. Herrell,[10] Randall,[11] Speert,[8] and others state that they have never seen fundal adenocarcinoma develop in the castrate woman. Clyde Randall is even more emphatic (too much so, we believe) in stating that he has never seen endometrial carcinoma develop in a woman whose vasomotor symptoms or

vaginal epithelium suggest estrogen deprivation. J. H. Randall[11] has, however, reported 4, Smith[13] 3, and Te Linde[33] 1 castrate individual who later developed adenocarcinoma. In all cases laparotomy confirmed the absence of ovarian tissue. Nevertheless adenocarcinoma developing post castration must be conceded to be rare.

6. More and more patients are being reported with a long history of estrogen therapy and later development of endometrial cancer. One of the authors (E. R. N.[14]) reported such a case recently, at which time a review of the literature revealed approximately fifteen well-authenticated cases. It should be emphasized, however, that, in view of the extremely wide usage (generally unwarranted) of estrogen therapy and the frequency of endometrial carcinoma, it would be unusual if the two did not coexist on occasion.

It is thus only natural that attention has been focused on the ovary, the normal source of estrogen in the menstruating woman. Although fundal adenocarcinoma is essentially a disease of the postmenopausal, nonmenstruating woman, this by no means contraindicates the ovary as a possible etiological factor. To our knowledge no satisfactory study of blood or urinary estrogens has been made in patients with fundal cancer. Should it be practical to carry out such a study and should this show a consistently low estrogen level, the ovary would still not be absolved as a possible inciting focus in the future development of adenocarcinoma. In view of our present ignorance of the course of cancer, it may not be unreasonable to assume that precancerous changes invoked by a stimulating agent may continue into true cancer even if the stimulus is removed.

It is established, however, that the urine of certain postmenopausal women may contain estrogen long after the menopause. Clinically it is by no means rare to find hyperplasia or a proliferative endometrium in a postmenopausal woman who has not received estrogen therapy and has no known feminizing tumor. This has been well demonstrated by Novak and Richardson,[15] and further studies will be reported in a future publication by Woodruff and Novak with particular regard to the later development of adenocarcinoma.

It is true that the adrenal gland has often been considered as a potential source of estrogen, and hyperplasia and/or urinary estrogen has been found in the surgically castrate woman. One must, however, be mindful of the difficulty of ascertaining complete ablation of all ovarian tissue in castrated women. (We have known personally in recent years of at least two women with breast cancer who have had oophorectomy without hysterectomy by general surgeons; one continued to have normal periods; the other had amenorrhea but due to pregnancy. In both instances, further surgery revealed residual ovarian tissue.)

We should like to direct attention to recent investigation on the morphology of the aging ovary with particular regard to its structure and possible function in endometrial carcinoma. This study by Woll, Hertig, Smith, and Johnson[16] has summarized the previous work of these and other authors in what we regard as an extremely interesting and provocative piece of work and will be referred to frequently in this paper. Among their conclusions is the significant frequency of ovarian stromal hyperplasia in adenocarcinoma of the fundus, as well as the high incidence of thecoma and diffuse thecomatosis.

The stromal cell in the menstrual era seems to fulfill two main functions: (1) as a connective tissue matrix for the Graafian follicles, (2) as probable progenitor of theca externa and possibly interna with the capacity to assume a lutein appearance and function.

Fig. 1.

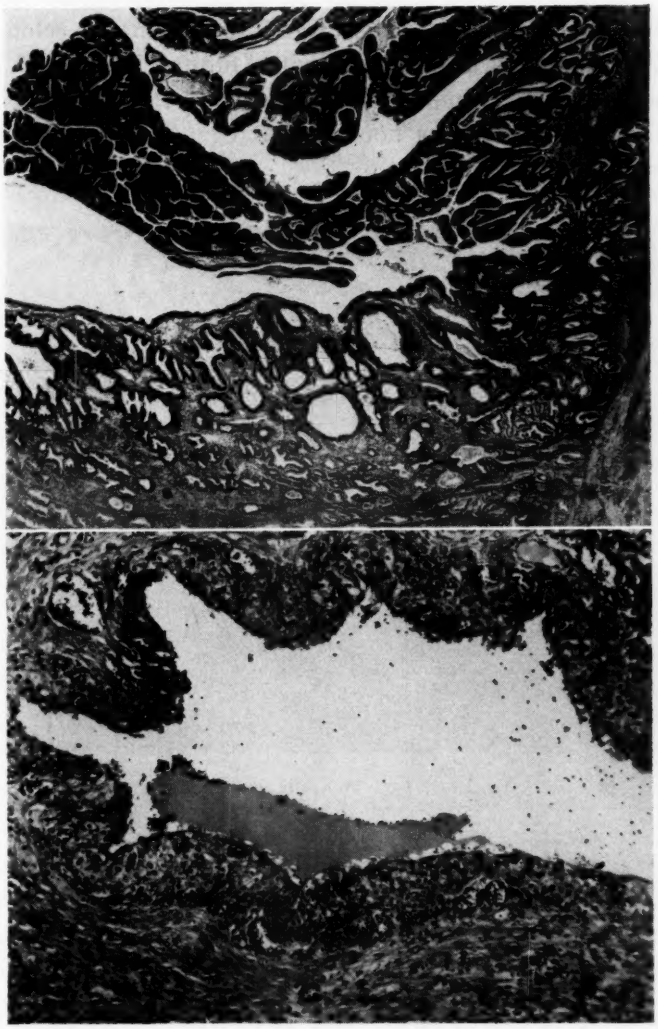

Fig. 2.

Fig. 1.—Adenocarcinoma above, hyperplasia below, with a secretory pattern on the right. This suggests that a generally progestational endometrium may contain certain unripe areas incapable of response to progesterone and thus subject to prolonged unopposed estrogen. This could explain the findings of Jones and Brewer.

Fig. 2.—Recent corpus luteum associated with Fig. 1. Patient is a 38-year-old para ii.

In so far as the endocrine function of the theca cell is concerned, there is considerable divergence of opinion. Certainly it seems that a theca-cell tumor may be estrogenic, and a number of cases have been reported in association with hyperplasia and/or clinical evidence of estrogenic activity. Indeed, some authors contend that granulosa-cell tumors are not feminizing per se, but only because of the admixture of theca cells which can usually be found.

On the other hand, one can find statements that the theca cell has in reality an androgenic function, and that theca-cell tumors may be feminizing "but only because of the admixture of granulosa cells to be found." This hypothesis is strengthened by reports of theca-cell hyperplasia in association with virilism. Shippel[17] in a subsequent publication contends that the ovarian theca and the testicular interstitial cell stem from the gonadal mesenchyme and are androgenic; the granulosa and Sertoli cells originating from the celomic epithelium are estrogenic. This thesis is in accord with Gunnar Teilum's[19] correlation of androgenic and estrogenic tumors of the gonad. Clinically it is definite that the urine of the female contains not only estrogen but androgen (supposedly from an adrenal source).

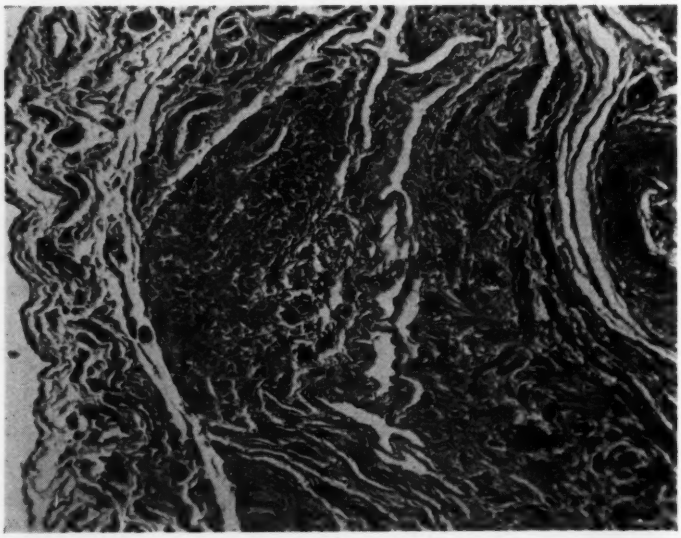

Fig. 3.—Clump of hilus cells in mid-left. The difficulty in distinguishing these from nerve fibers, walls of blood vessels, etc., may be apparent even here.

Of interest is the work of Hertig and Sommers,[21] and Dockerty, Lovelady, and Foust,[20] whose study of the ovary in young premenopausal patients with endometrial cancer showed a considerable number to have ovarian pathology and clinical features compatible with the so-called Stein-Leventhal syndrome. These ovaries were generally grossly enlarged and cystic with a thickened tunica. Stromal-cell hyperplasia was present in a significant proportion. Clinically such patients often show amenorrhea or oligomenorrhea, hirsutism, an enlarged clitoris, and sterility, which features must be regarded as suggestive of at least defeminization, if not virilism. Dockerty shows photomicrographs of hyperplastic stromal cells whose appearance is not dissimilar to theca cells. Leventhal and Cohen[22] suggest that the ovary is the seat of androgen production and imply that progesterone, apparently produced by theca cells, may exert an androgenic action.

It seems apparent that the function of the stromal and the theca cell is the source of considerable confusion; indeed, the histology of the ovary and its various component cells is poorly understood. Among the other more bewilder-

ing aspects is the status of the so-called hilar, interstitial, or Leydig cells, often seen in the hilus of the ovary presenting as clumps of large, pale, polyhedral, often eosinophilic-staining cells (Fig. 3). They were described by Berger[23] in 1922 and considered as sympathicotropic in nature, although previous investigators (His, 1865, and others) had apparently described these cells in animals. Shaw and Dastur[24] (1949) have suggested that such cells are found frequently in association with endometrial cancer, and, even before their publications, we at Hopkins were observing these cells in connection with fundal lesions but did not know how to interpret them.

Shaw and Dastur found these cells in approximately 50 per cent of 48 cases of endometrial cancer but only rarely in a control group and felt that they are probably carcinogenic by virtue of a hormonal influence. Four cases are reported in detail. They comment on the hilar location with a tendency toward diffuse spread into the medullary area with recognition so difficult that an erroneous impression as to frequency may be held. They believe these cells to originate from the endothelium of the immediately adjacent blood vessels.

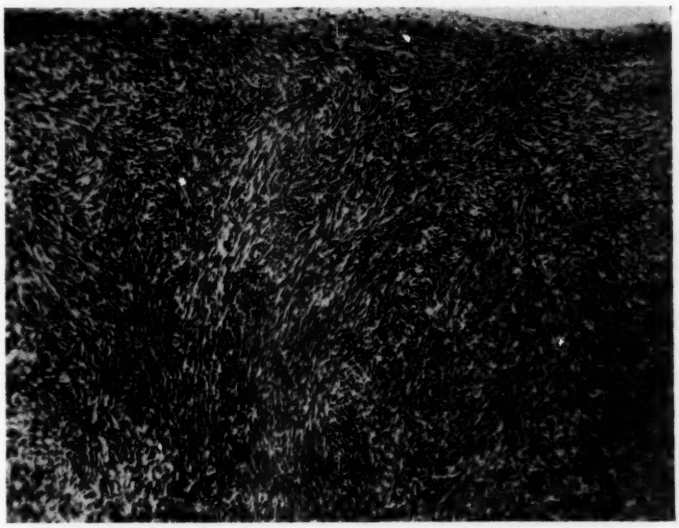

Fig. 4.—Fibrotic ovary to left with transition to hyperplastic area on lower right with large, plump, pale cells (patient 63 years old and 11 years postmenopausal).

Green and Peckham,[25] however, belittle the importance of these cells and feel that they occur with equal frequency in adenocarcinoma and control groups, and in direct proportion to the thoroughness of the study.

Should one be inclined to consider them as possibly estrogenic in nature and akin to the feminizing tumors, he should be heedful of the fact that there are no less than six well-authenticated cases of hilus-cell tumors in association with clinical virilism. The difficulty in distinguishing hilus, adrenal, and luteinized theca cells is a real histological problem, and one should always be properly critical in accepting reports of such cases.

It seemed distinctly worth while to us to repeat the study that was carried out by Woll, Hertig, and co-workers and try to evaluate the ovarian histology in cases of endometrial cancer. We decided to limit our cases to the post-

menopausal group (at least one year after the last period), because we feel that proper evaluation of stromal hyperplasia in a premenopausal, physiologically active ovary might be inaccurate and misleading. Second, we decided to confine our cases to those in whom preoperative irradiation was not used, believing that either x-ray or radium might occasionally influence ovarian architecture. We chose our material from the files of the Bon Secours Hospital where the patients are all white, predominantly private, and until recently treated surgically with later x-ray therapy. After discarding previously irradiated patients, premenopausal patients (seven in number), and cases where the microscopic sections or clinical material seemed inadequate, we emerged with a total of 63 cases. As controls, we studied the ovaries of women autopsied by the Pathology Department at the Johns Hopkins Hospital, selecting only postmenopausal white women in decades similar to those in carcinoma cases. Care was taken to avoid individuals with abdominal carcinomatosis, overt endocrine dysfunctions, or long debilitating illnesses, and to the best of our knowledge this control group is completely representative and unselected.

Clinically our cancer patients showed the following characteristics, all of which have received previous comment by many observers:

A. Age incidence at discovery of cancer—59 years.

B. Delayed menopause—average age slightly over 51 years, including six patients who were given an irradiation menopause, two in their thirties. Even including these, 50 per cent had their menopause after 50 years of age.

C. Parity—exactly one-third were nulliparous; of the remainder various parity up to twelve was found.

D. Abnormal menopause—slightly more than one-third (23 patients) admitted or knew of bleeding abnormalities in earlier years. Fourteen of these had received previous treatment in the menopausal era.

E. Previous irradiation—six of the patients, or less than 10 per cent, had received previous irradiation for benign bleeding, half by x-ray, half by radium.

F. Estrogen therapy—in only three cases was this noted, but since much of our information was from an intern's history where direct query may have been omitted, the actual figure is probably considerably higher.

G. Medical diseases—obesity (more than 150 pounds) was found in 45 per cent, hypertension (more than 140/90) in 48 per cent, and clinical diabetes was found in 18 per cent. (These criteria are of course arbitrary.)

In attempting to evaluate the ovaries in our series, we tried to interpret the appearance of the individual cell as well as the degree of stromal hyperactivity. Obviously this grading is subjective, but every attempt was made to be accurate and unprejudiced. In most instances only one section of ovary was available and on occasion the block included only a part of the hilar area. We graded the ovary from a zero to a Grade 3 in regards stromal hyperactivity; this is probably not precise but we feel that the Grades 0 and 1 (little or no activity) are very different from the Grades 2 and 3 (marked activity).

Our small series seems to confirm the previous work of Woll, Hertig, and associates in respect to the preponderance of ovarian stromal activity in the carcinoma group. This change was sometimes quantitative, in that most of the stroma appeared hyperactive, but was more commonly diffuse and patchy, suggesting focal hyperplasia rather than diffuse hyperactivity (Fig. 4). We were impressed in particular by the appearance of some of these postmenopausal stromal cells. Instead of a small dark-staining spindle type of cell, it was com-

mon to observe a plump, large, paler-staining, epithelial type of cell. It was most commonly found in whorllike clumps in the cortex with occasional extension into the medullary portion. Resemblance to theca, and at times even lutein or paralutein cells was striking (Fig. 5). This "diffuse thecomatosis" seemed closely akin to a true thecoma, the diagnosis being withheld only by lack of a capsule, the diffuse nature of the process, etc. Since these cell changes seemed merely an extreme response in a generalized process, we did not make a separate group of such instances, using the term stromal hyperactivity for all (Fig. 6).

Fig. 5.

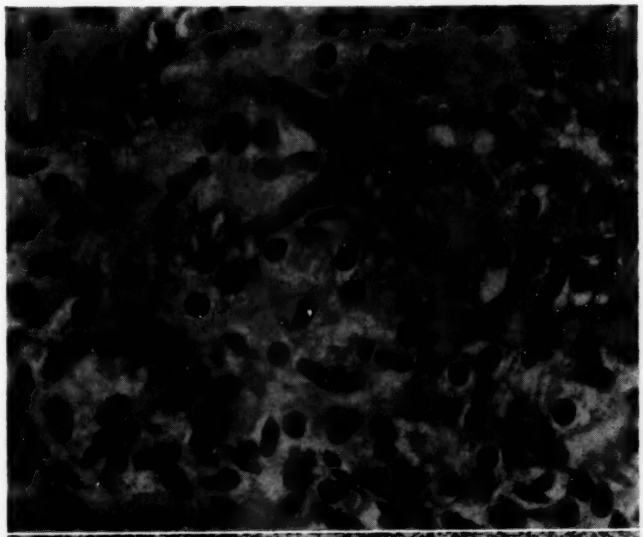

Fig. 6.

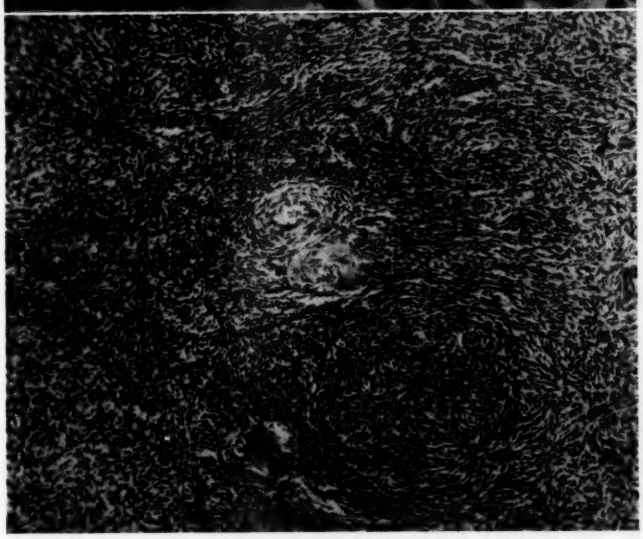

Fig. 5.—High power of hyperplastic cells which are large, polyhedral, and have appearance of theca cells.

Fig. 6.—Small focus of hyperactivity surrounding and particularly below blood vessels. Contrast with senile appearance at right (59-year-old patient who is 8 years postmenopausal).

Table I shows the incidence of ovarian stromal hyperactivity in the cancer and control series arranged in the different decades. Probably the individual number in each group is too small to be valid. Of the whole group of 63 cancer

patients, however, only 29 (46 per cent) had minimal stromal changes while 34 (54 per cent) had marked degrees. Forty-eight (78 per cent) of the control group had an essentially atrophic gonad, while 15 (21 per cent) had hyperactivity.

TABLE I

DECADE	NO. OF PATIENTS	LITTLE OR NO STROMAL HYPERPLASIA (0-1)		SIGNIFICANT STROMAL HYPERPLASIA (2-3)	
		CA	CONTROL	CA	CONTROL
45-54	16	4 (25%)	12 (75%)	12 (75%)	4 (25%)
55-64	33	18 (55%)	27 (82%)	15 (46%)	6 (18%)
64 and over	14	7 (50%)	9 (64%)	7 (50%)	5 (36%)
All ages	63	29 (46%)	48 (79%)	34 (54%)	15 (21%)

It may be noted that our percentage of stromal hyperplasia in both groups is somewhat lower than Woll, Hertig, and co-workers have reported. We should like to reiterate that the grading is subjective and feel that the important fact is our concurrence in the more than double predominance of hyperplasia in the cancer patients. In addition our patients were uniformly postmenopausal, which the earlier series was not.

We then decided to attempt to correlate the degree of stromal hyperactivity with the histologic grade of tumor. Results were not really conclusive but suggested that marked stromal changes were present predominantly in the lesser grades of cancer (Table II). We have no satisfactory explanation for this; perhaps it represents variations in the endometrial response, but in our rather few cases of Grade III and IV tumors, stromal activity was not a striking finding.

TABLE II

GRADE OF CA	NO. OF PATIENTS	NO. WITH ACANTHOSIS	STROMAL HYPERACTIVITY	
			LITTLE OR NONE	MARKED
I	13	6	8	5
II	28	13	7	20 (1 granulosa and 1 theca cell)
III	15	1	9	6
IV	7	0	6	1

We feel that this is at odds with the hypothesis suggested by Woll, Hertig, and collaborators, as to the ovarian-endometrial relation in fundal carcinoma. They suggest that catabolic changes in the endometrium mediate the ovarian changes through the pituitary. It would seem probable to us that the more extreme grades of adenocarcinoma should be associated with more marked catabolic activity and thus lead to profound pituitary stimulation with resultant ovarian stromal changes. This was certainly not found and although no one can be dogmatic, we believe that all available evidence suggests that the ovarian changes, if not primary and possibly of etiological import, are not secondary to endometrial catabolism. In this we concur with Sternberg and Gaskill[28] who expressed the same disagreement in their recent article on thecomas.

The apparent high coexistence of acanthosis with stromal hyperplasia is probably simply due to the prevalence of metaplasia in the less advanced grades of tumor, for attempts to correlate adenoacanthoma with ovarian changes re-

vealed nothing except to confirm the already accepted fact that it is significantly more common in the well-differentiated (approximately 45 per cent) than in the more advanced grades (less than 5 per cent) of adenocarcinoma. We feel that this may be due to the incapability of the very active undifferentiated tumor cell to undergo metaplastic changes that as a rule lead to a rather adult form of squamous cell. This seems more probable than the theory that "indifferent resting cells undergo acanthotic transformation." It is not rare to see actual transition forms between the usual lining epithelium cells and typical epidermoid structures (Fig. 7). Apparently they in no way affect the prognosis, other than to indicate a tumor with good differentiating capacity.

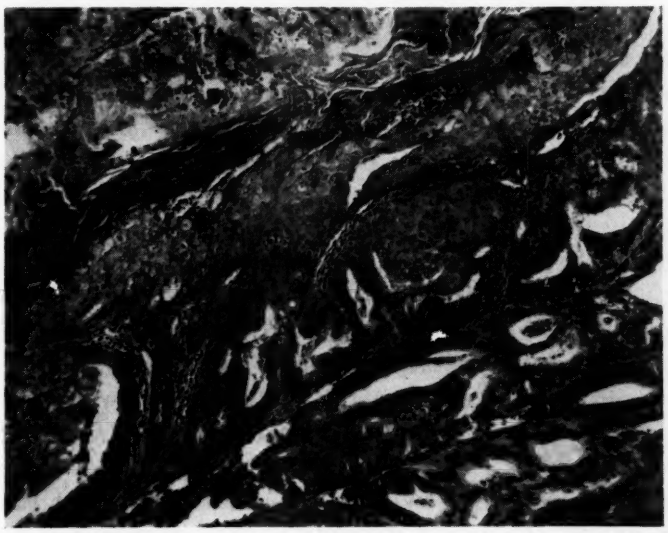

Fig. 7.—Adenoacanthoma Grade I. Close study will reveal all intermediate transition forms from lining glandular epithelium (below) to mature squamous forms (above).

Hilus cells were found in approximately equal amounts in the two series, seven in the cancer and six in the control group. It should be emphasized that in most instances only one section of ovary was available for study, and the uniform experience in finding these clumps of cells indicates their presence is in proportion to the number of sections studied. Furthermore the work of Husslein[26] suggests their decreasing frequency in the postmenopausal era. However, we feel that we can conclude that these hilus cells seem no more common in the adenocarcinoma than the control group, all postmenopausal.

The tumor group included one granulosa-cell and one theca-cell tumor; the control group revealed neither. We found various remnants of the rete testis and mesonephric duct, Brenner rests, simple cysts (generally germinal inclusion), etc., in comparable amounts in both groups, and feel strongly that their presence is purely coincidental. The so-called cortical granulomas were never impressive in either series.

Seemingly our study provides further confirmation that the ovary found in conjunction with endometrial adenocarcinoma has certain histological differences from the usual postmenopausal gonad. The high incidence of stromal

hyperplasia with thecalike changes is a striking, if not a constant finding. More complete sections of the ovary in fundal cancer might well reveal a much greater percentage than reported here.

There were several interesting findings in the control series with marked degrees of stromal hyperactivity, and we should like to state that we examined and graded the histological sections before consulting the protocol for autopsy findings. Six patients had died with breast cancer, and four of these cases showed ovarian activity. This is in keeping with the report by Sommers, and Teloh,[27] although our total number of such cases is too small to be significant.

Of additional interest was the frequency of obesity, hypertension, and diabetes in the noncarcinoma control patients with marked degrees of stromal hyperactivity. One might assume that activity of the ovarian stroma is often associated with a widespread metabolic or endocrine imbalance, with fundal adenocarcinoma a frequent though not inevitable concomitant. Whenever there is generalized endocrinopathy, the pituitary is always suspect because of the multitude of "tropic" hormone, but its location in the sella turcica makes study and proof a difficult problem.

We personally feel that there is extremely suggestive evidence that estrogen is the inciting factor to fundal adenocarcinoma in the predisposed postmenopausal patient. Previous mention has been made of the various approaches suggesting the importance of hyperestrogenism. Histologically the thecalike stromal cells would appear to be a very logical source for secretion of such a hormone. Fat stains were performed on only a few of the ovaries with equivocal results. On occasion, these thecalike cells seemed to take the stain brilliantly, yet at other times poorly.

It has been reported that activity of the pituitary FSH or LH can produce stromal hyperactivity. Certainly it seems possible that sustained hypophyseal stimulation may transform the resting stromal cell into an active agent capable of activating the endometrium. Although this seems logical to us there is no direct proof nor explanation as to what might incite the pituitary to abnormal stimulation.

One may be inclined to consider the work of the Biskinds,[29] and others who grafted ovaries into the spleen with a resultant portal shunt and consequent inactivation of estrogen. Granulosa-cell proliferation and tumors followed, presumably due to the unopposed action of the gonadotropic substance on the ovary. From this we may deduce that various generalized metabolic or endocrine disorders that alter the metabolism of estrogen or otherwise disturb the endocrine imbalance might affect the pituitary. Liver disease and vitamin deficiencies, among others, have been studied, without unanimity of opinion. We should like to add to this prospectus for further study the possible role of exogenous obesity.

All clinicians see fat women with amenorrhea often interspersed with episodes of menorrhagia of an anovulatory type. It is common experience to find that simple weight reduction by dietary measures alone may bring a return to normal menses, ovulation, and even pregnancy. Obviously obesity is not carcinogenic per se; we see too many healthy, happy fat women. As a possible

agent in the influence of anovulation, hyperestrogenism, and a possible generalized endocrine imbalance, it does seem to deserve further study. A recent study by Rogers and Mitchell[30] has confirmed our impression as to the high frequency of obesity and menstrual disorders and they have re-emphasized the possible importance of a hypothalamic-hypophyseal role.

At this stage of our knowledge no one can be dogmatic as to the evolution of fundal cancer, but it seems that ovarian stromal hyperplasia is found in a high percentage of the cases, and that this might well serve as a source of sustained estrogenic substance. One can do no more than conjecture as to the etiology of the stromal changes, but it is felt that the pituitary is of considerable importance in either a primary or secondary role.

Conclusions

1. Numerous publications from diverse angles suggest that prolonged unopposed estrogen stimulation may be of importance in the evaluation of endometrial cancer. Thus the usual source of estrogen, the ovary, warrants careful scrutiny, even in the postmenopausal woman.

2. Hilus cells, as well as simple cysts, Brenner or Walthard rests, mesonephric and rete testis remnants, etc., seemed to occur with equal frequency in the older woman with and without fundal carcinoma.

3. The previous publications in regard to the increased incidence of ovarian stromal-cell hyperplasia in association with adenocarcinoma of the fundus have been confirmed. Fifty-four per cent of our tumor group showed such changes as opposed to 21 per cent of the control group.

4. The qualitative changes in the ovarian stromal cell were more impressive to us than the quantitative; in particular, the apparent conversion of the atrophic postmenopausal stromal cell to a plump hyperactive thecalike cell with a histologically suggestive endocrine function.

5. The possible importance of stromal-cell hyperactivity as part of a generalized endocrine or metabolic imbalance is discussed with particular reference to the uncertain role of the pituitary.

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26 East Preston Street

THE STUMP-STITCH TECHNIQUE FOR VAGINAL HYSTERECTOMY

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ONE of the most challenging problems in vaginal hysterectomy is the matter of achieving the hemostasis of the parametrium. Frequent use is made of clamps which are subsequently replaced by ligatures, but the great disadvantage inherent in this method is that the clamps will crush previously that area of the tissue which should be kept in perfect condition in order to serve as reliable stumps. Furthermore, when the clamp is replaced by a ligature, it is necessary to cut the parametrium before it is ligated; and if some tissue should slip out of the ligature loop or if the replacing ligature should break, it might be very difficult to control the resulting hemorrhage in the narrow operating field—difficult and dangerous, too, because of the proximity of the ureter.

It is unquestionably much safer to ligate the parametrium before dissecting it. However, the ligatures must not be tied and placed in the line of dissection, as is so commonly and so erroneously done, whether or not clamps are used. Tapering stumps, slipping ligatures, loosening of the ties, escaped tissue, retracted stumps, and unligated areas are the consequences of this faulty technique (Fig. 1). The transverse cut which has been recommended for the prevention of defective hemostasis[1] in dissecting a bridge of tissue is very useful in performing an abdominal hysterectomy, but not suitable for the vaginal route. This is true because the parametrium, being under tension as the result of traction on the uterus, might tear in the direction of the transverse cut.

A technique was therefore developed which makes it possible to place the ligatures correctly, close to each other, without making the transverse cut. The technique, which I call Stump-Stitch Technique, may be demonstrated on two consecutive sutures (Fig. 2). The first suture ligature (*L1*) is tied around the free margin (M) of the bridge of tissue. A reliable stump (*S-1*) is readily formed. The second suture (*L2*) encircles the following portion of the tissue (*S-2*). The basic idea of the stump-stitch technique consists in placing the second ligature close to the previous one by passing the needle through the first stump in the opposite direction. The simple procedure of anchoring the ligature by passing the needle somewhere, as at *X*, through the previous stump (Fig. 2, *I*) but not close to the previous stitch canal (*C*), would, indeed, prevent the ligature (*L2*) from slipping, but the hemostasis would be defective (Fig. 2, *II*). It is essential that the needle be passed through the stump extremely close to the previous stitch canal (*C*) (Fig. 2, *III*) in order to eliminate unligated areas between the ties (*L1*) and (*L2*) (Fig. 2, *IV*).

The stump-stitch technique offers the advantages of:

1. Forming reliable stumps of uncrushed tissue.
2. Preventing the ligature from slipping.
3. Cutting the tissue *after* it has been ligated.
4. Dissecting the parametrium extremely close to the uterus.
5. Eliminating unligated areas.

The Stump-Stitch Technique for Vaginal Hysterectomy

A quarter length of chromic catgut No. 1 on a large needle is used for the suture ligatures. After the posterior cul-de-sac has been opened, the first needle encircles the uterosacral ligament. The ligature is tied but—and this is important—only about one-half of the ligated tissue is dissected. The next

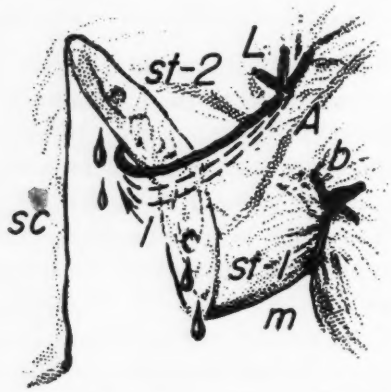

Fig. 1.—A common error. The first ligature around the stump (*st-1*) is correct. The second ligature (*L*), however, is incorrectly placed into the gape of the separating cut (*sc*). The resulting stump (*st-2*) is tapering, the ligature (*L*) slipping, and the loop (*l*) getting loose. Furthermore, the area (*A*) is not ligated. The resulting danger of bleeding from the second *and first* stump is obvious.

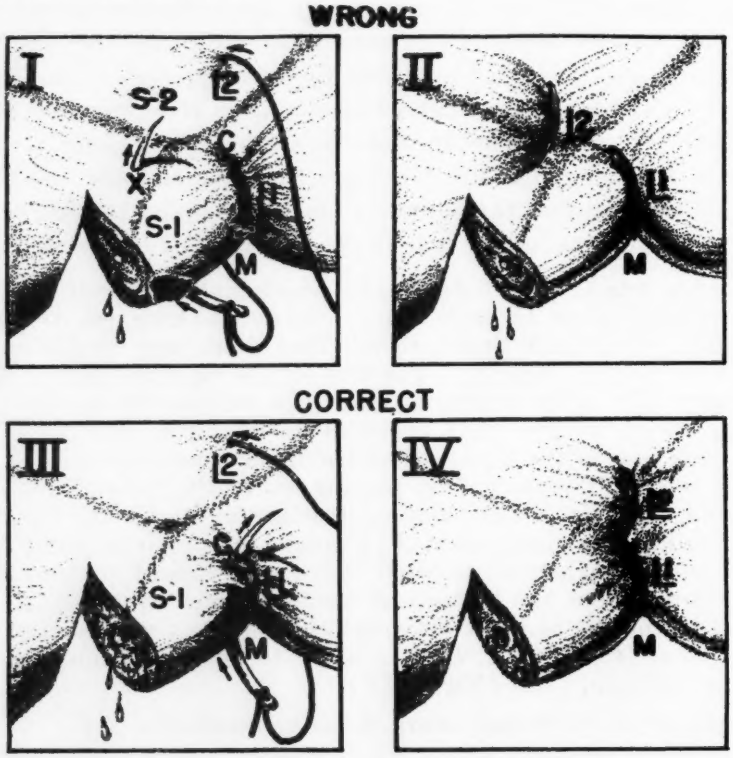

Fig. 2.—The wrong and the correct stump stitch.

I. The needle is passed through the first stump (*S-1*), but incorrectly at the point (*X*).

II. The area between (*L1*) and (*L2*) remains unligated and the danger of bleeding from the *first* stump is obvious.

III. The needle is passed through the first stump (*S-1*), correctly close to the first stitch canal (*C*).

IV. No unligated area remains between the ligatures.

suture is applied to the following portion of the parametrium in anteroposterior direction (Fig. 3). However, instead of placing the ligature erroneously in the line of dissection, the same needle is passed through the first stump extremely close to its ligature, but in the opposite direction (Fig. 3). This is easily accomplished because the first portion which has previously been ligated had been only partly dissected. The idea of the incomplete dissection of the ligated tissue is that simple traction on the uterus will expose the ligature.

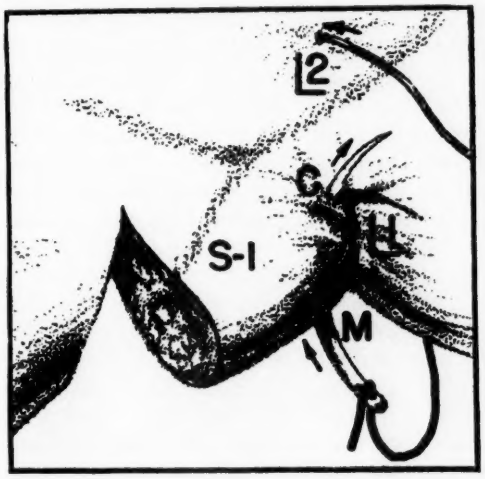

Fig. 3.—Ligation of the parametrium. The second ligature is passed through the entire thickness of the uterosacral ligament close to the stitch canal (*C*) of the first ligature (*L1*).

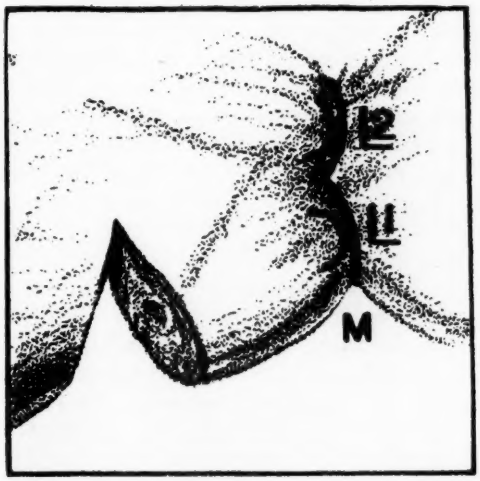

Fig. 4.—The knots of the ligatures are tied in front of the tissue.

Thus the point where the needle of the following suture ligature should pass the entire thickness of the stump can be determined with utmost precision. That would be very difficult or nearly impossible if the retracted stump had to be exposed with a forceps or a clamp.

The remainder of the first ligated portion of the tissue and about half of the second portion are then dissected very close to the uterus. It is an important detail of this technique that the suture ligatures for the parametrium and the adnexa are started in anteroposterior direction and are concluded in the opposite direction in order to tie the knots in front of the tissue (Fig. 4).

After the uterosacral ligaments and the lower portion of the cardinal ligaments have been dissected on both sides, the peritoneal bladder reflection is opened. The next needle should transfix first the avascular area of the broad ligament and then the cardinal ligament below the uterine artery. The ligature is then tied, but the uterine vessels are not dissected until the same procedure has been performed on the other side. Now both uterine arteries are dissected. Postponement of the separation of one uterine artery until the other one has been ligated eliminates a great deal of reflux bleeding.

Now the fundus of the uterus is favorably moved into the vagina. A suture ligature is placed around the tube and the ovarian ligament. The next needle is passed first through this stump, then the same needle encircles the round ligament and the upper portion of the broad ligament. The ligature is tied in front of the broad ligament and the separating cut extended. The next suture ligature is passed through the stump of the round ligament close to its ligature; the same needle encircles the entire remainder of the broad ligament, and is finally passed through the cardinal ligament below the uterine artery which is advantageously included in this tie. The rest of the parametrium is dissected and the uterus entirely separated on one side. The same procedure is performed on the other side, where several backhand stitches might be necessary in order to tie the knots in front of the ligated tissue. After the uterus has been removed the operation is concluded in the routine way.

An important point which prevents the parametrial ligatures from getting loose is that the square knots which consist of two parts must be flat *at any stage* of the tying maneuver. It is not enough that the examination reveals that the *completed* knot is flat. If the first part is twisted during the tying maneuver the ligature will break; and a twisted second part will loosen the first knot. Crossing the hands or the fingers *after* tying, as is frequently done, in order to "straighten out" the twisted knot, does not eliminate the destructive effect of the twist on the ligature during the tying maneuver. The analysis of the square-knot technique reveals that this unfavorable twisting can be avoided only if the ligature is crossed each time *before* one part is tied. As the square knot consists of two parts, the ligature must be crossed twice. This can be accomplished by a maneuver which is called "changing hands." That means that the right hand takes the end of the ligature from the left hand and vice versa. "Changing hands" is time consuming, and though it is an excellent and safe method for tying a correct square knot under tension it is not convenient and not recommended for ligating the parametrium.

The anatomy of the parametrium and the adnexa makes it possible to apply and tie their ligatures in the course of a vaginal hysterectomy in the *sagittal* plane. And this, in turn, makes it possible to cross the ligatures in a very simple manner, which I call the "passing maneuver," meaning that the hands holding the ends of the ligature pass each other by moving up and down in opposite direction, whereby the ligatures are correctly crossed immediately before being tied. The passing maneuver eliminates the time-consuming "changing hands," as well as the clumsy and disadvantageous crossing of the hands or

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Fig. 5.—The fast square knot in the sagittal plane.
A, Right down position: right hand down, left hand up.
B, The first triangle (*T*).
C, The left index finger is moved into the triangle from above down.
D, The right middle finger hooks and pulls the ligature through the loop.
E, The thumb assists the middle finger to catch the end of the ligature.
F, The knot is tightened by concluding the passing maneuver.
G, Left down position: left hand down, right hand up.
H, The second triangle (*T2*).
I, The left index finger has moved into the triangle *from below up*.
J, The right index finger ties the knot and pulls the ligature through the loop.
K, The thumb cooperates with the index finger to catch the end of the ligature.
L, The knot is tightened by completing the passing maneuver.

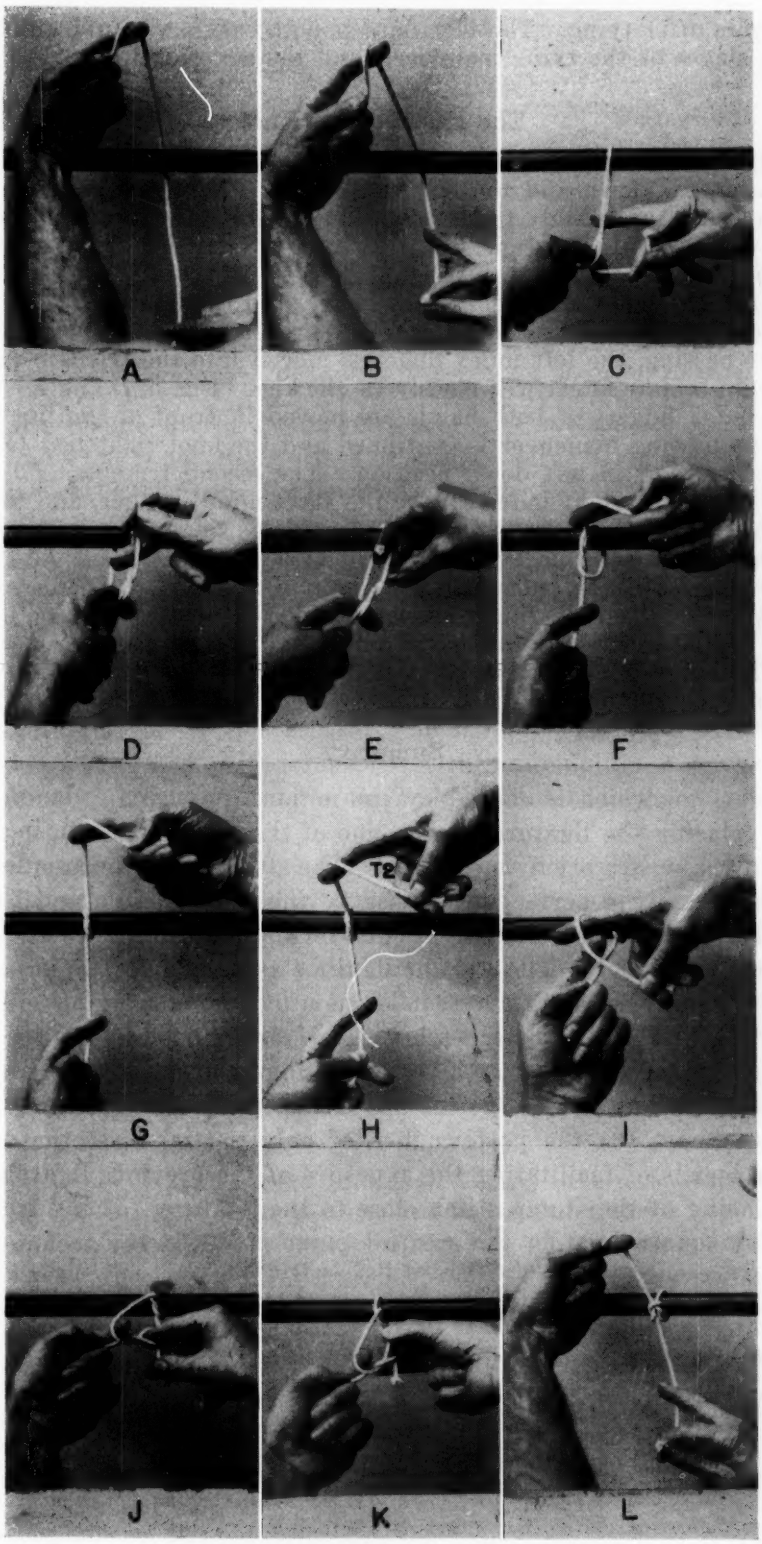

Fig. 5.—*For legend see opposite page.*

of the fingers *after* tying. The technique is both easy and rapid, the ligature is flat at all stages of the tying maneuver, and the end result is a reliable square knot.

The Fast Square Knot

The tying maneuver may be started in two different positions. In Fig. 5, *A*, the right hand is down and the left hand is up. This position is called *right down* position. Accordingly the left hand down and the right hand up is called *left down* position. In the right down position the stretched right middle finger is placed in front of the ligature (Fig. 5, *B*). A triangle (*T*) is created between the right middle finger, the right index finger, and the ligature. The left index finger is *on the same side* of the ligature as the right middle finger. At the moment of passing, the left index finger is moved into the triangle (Fig. 5, *C*) and the right *middle* finger will readily tie the knot (Fig. 5, *D* and *E*). Immediately the index fingers of both hands are moved in front of the ligature (Fig. 5, *F*). The passing maneuver is continued and the knot tightened (Fig. 5, *G*). The hands are now in left down position. The second triangle (*T2*) has been created between the right index finger, the right middle finger, and the ligature (Fig. 5, *H*). On passing, it is again the left index finger which moves into the triangle, this time, however, upward from below (Fig. 5, *I*), and the right index finger is ready to tie the knot quickly (Fig. 5, *J* and *K*). Immediately the left index and the right middle finger are moved in front of the ligature, the passing maneuver is continued, and the second half of the square knot is tightened (Fig. 5, *L*). The hands are again in right down position as in Fig. 5, *B*, ready for another knot if desired.

Summary

The damage which is caused by the action of crushing clamps, and the danger of placing the ligatures in the line of the separating cut, in dissecting a bridge of tissue, are briefly mentioned. The stump-stitch technique is recommended for achieving perfect hemostasis of the parametrium and the adnexa in vaginal hysterectomy. The stitch must be applied through the entire thickness of the stump and as close to the ligature as possible. The importance of making flat square knots is stressed. A new technique of tying square knots with the ligatures of the parametrium is presented. New features are: (1) The elimination of unligated areas in dissecting a bridge of tissue by stitches through the previous stump, (2) the use of the stump-stitch technique in vaginal hysterectomy, (3) the performance of only partial dissection of ligated tissue as a means of facilitating the exposure of the previous ligature, (4) the regular placing of the stump stitch close to the ligature, (5) the technique of tying a flat square knot in the sagittal plane, and (6) the technique of the passing maneuver.

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ROUND-CELL SARCOMA OF THE UTERUS

Report of a Case

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SARCOMA of the uterus is an extremely rare malignant disease. Novak and Anderson reported 59 cases of uterine sarcoma in a series of 26,973 gynecologic specimens, an incidence of 0.22 per cent, and this number of cases constituted 4.5 per cent of the uterine malignancies exclusive of chorionepithelioma. Evans, considering the material of the Mayo clinic, found one sarcoma of the uterus to forty cancers. Cohen and Cravotta in reviewing cases from the Elizabeth Steel Magee Hospital and University of Pittsburgh disclosed 16 cases of sarcoma of the uterus in 23,859 gynecologic cases, 2.6 per cent of all malignancies of the uterus.

Sarcomas may be divided according to the point of origin or according to the cell type. The point of origin may be in the musculature or connective tissue of the uterine wall, in the stroma of the endometrium or in a previously existing myoma.

If the tumors of the uterine corpus are classified according to cell type, we find spindle-cell, round-cell, and mixed-cell varieties, while in the rare round-cell sarcoma of the cervix, which occurs in the crevix more often in children, there may be an admixture of cellular elements which betoken an embryonic influence. The proportions given by Weil in his Inaugural Dissertation are as follows: (1) spindle cell (seldom pure, but mostly preponderating) 35 per cent; (2) round cell, 40 per cent; (3) mixed cell, 25 per cent.

The following case of a round-cell sarcoma of the uterus is reported because of its rare incidence.

Mrs. S. W., a 56-year-old white nulliparous woman, come to my office December 1, 1950, complaining of pains in the paraumbilical region and a bloody vaginal discharge, weakness, and loss of weight. She had never seen a doctor in all her life though she had chronic sinus trouble. The patient had had the menopause 6 years before. Three years later she started to have moderate vaginal bleeding of bright red blood on and off. One year and a half before admission she started to have a watery discharge that gradually became foul with passing of chunks of necrotic tissue during the last six months. She had lost a great deal of weight and strength and the fear of cancer prevented her from seeing a doctor. Her father died of cancer of the liver and her sister died of cancer of the breast.

Physical examination disclosed the presence of a small incarcerated umbilical hernia. There was a mass, paipable, that filled the lower part of the abdomen and seemed to extend from the pelvis. Pelvic examination showed a nulliparous introitus, necrotic tissue and polyp extruding from the cervical canal. A large, fairly fixed mass was felt to fill

the pelvis and extend from the lower abdomen up to the umbilical region. There were no nodules palpable in the mass or in the regional glands. A complete blood count disclosed: red blood cells, 4.15 million; hemoglobin 11.4 Gm., 73 per cent; white blood cells, 11,600; differential, Stab forms 1, segmented neutrophils, 80, lymphocytes 14, monocytes 5. The urine was essentially negative except for 2 to 3 red blood cells. The sedimentation rate was 61 mm. in 60 minutes.

A diagnostic curettement on Dec. 2, 1950, was reported as undifferentiated carcinoma, probably arising from the cervix.

An exploratory laparotomy was done on Dec. 4, 1950, with a preoperative diagnosis of (1) possible adenocarcinoma of the body of the uterus; (2) small incarcerated umbilical hernia. There was a large, boggy tumor of the uterus about the size of a 4 months' pregnancy filling the entire pelvis and the right side revealed a large hydrosalpinx. The right ovary was degenerated and attached to the distal portion of the hydrosalpinx was the small intestine. The left tube appeared normal. The left ovary was small and atrophic and lying deep in the cul de sac. The liver appeared to be normal. A panhysterectomy was done.

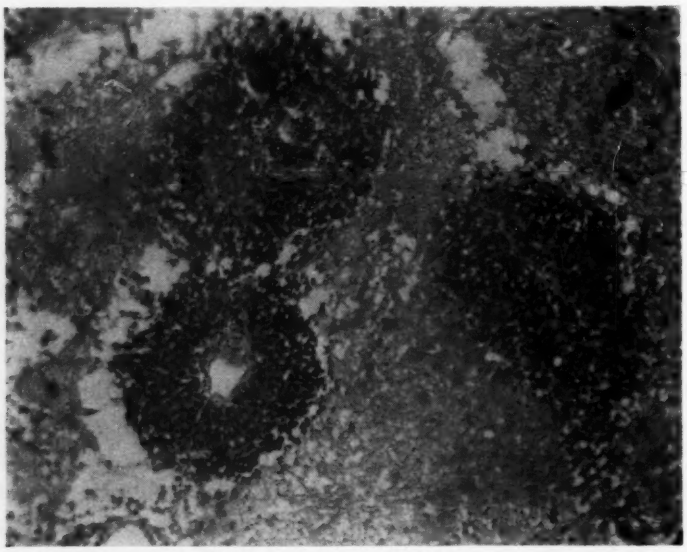

Fig. 1.—Photomicrograph of a section taken from a case of round-cell sarcoma of the uterus. This section shows cellular neoplasm composed of small round cells around small blood vessels with disintegration of cells in the periphery. (×100. Reduced one-fourth.)

The pathologic report was as follows:

Gross.—The specimen included a large uterus with tube and ovary attached on the right side and a tube and ovary detached. The uterus measured 11 by 17 by 10 cm. The outer surface was dark reddish in color and presented several fibrous-appearing adhesions. The cervix measured 3 by 3.5 cm. On the upper lip, the cervix presented a slightly raised hard area which was roughly oval in shape and measured 0.5 by 0.75 cm. The epithelial surface was pinkish gray and granular in appearance, overlying this region. When multiple cross sections were made through the uterus, the uterine cavity was found to be filled and distorted with a light yellowish-gray focally hemorrhagic, necrotic tumor mass, grossly resembling an infected fibromyoma with degeneration, necrosis, and hemorrhage. On the periphery, there was still found normal-appearing myometrium. The ovary was small, measuring 2 by 2.5 cm. It was firm and fibrotic in appearance. Neither ovary presented any gross changes of significance. Representative sections of the uterus, cervix, Fallopian tubes, and ovaries were taken for histologic study.

Microscopic.—Section through the cervix showed that the endocervical lining was diffusely and intensely infiltrated with lymphocytes, plasma cells, polymorphonuclear leukocytes, and a moderate number of eosinophils. The subjacent fibromuscular stroma was also infiltrated with inflammatory cells, sometimes found in focal collections. The stratified squamous epithelium was not seen in the sections studied and there was no evidence

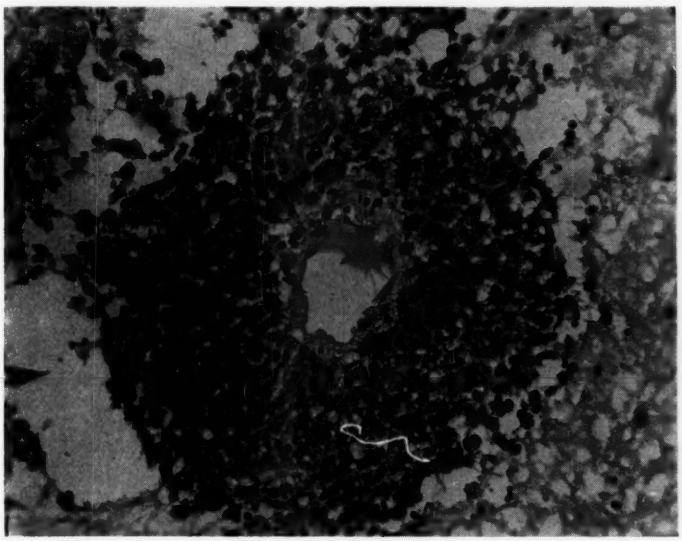

Fig. 2.—Photomicrograph showing details of malignant cellular arrangement about blood vessel with cellular disintegration in the periphery. (×300. Reduced one-fourth.)

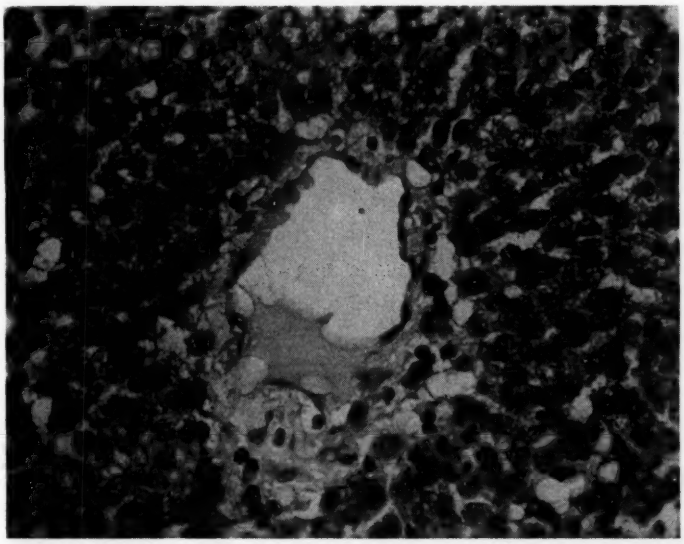

Fig. 3.—Photomicrograph showing perivascular details of round-cell sarcoma. The cells vary in size somewhat and present vesicular nuclei. Hyperchromatic nuclei and mitotic figures are also encountered. (×500. Reduced one-fourth.)

of malignancy of the cervix found in the sections observed. Sections through the tumor mass of the uterus described revealed a very cellular neoplasm comprised of small round cells frequently arranged around small blood vascular channels. The cells varied in size somewhat and presented vesicular nuclei. Numerous nucleoli were found in many of the cells examined. There were hyperchromatic nuclei and mitotic figures also encountered.

The intervening stroma, which in some places was fibromuscular in character, showed edema and degeneration. There also was a slight cellular infiltration with inflammatory cells found in these regions. The subjacent myometrium was also found to be infiltrated by neoplasm presenting the characteristic of that just described. Sections through the

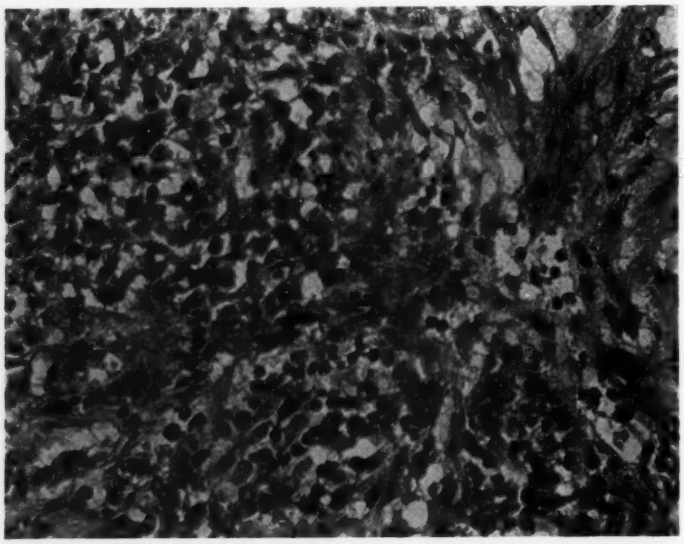

Fig. 4.—Photomicrograph of a section of round-cell sarcoma in which intervening stroma in some places is fibromuscular in character, showing edema and degeneration. (×400. Reduced one-fourth.)

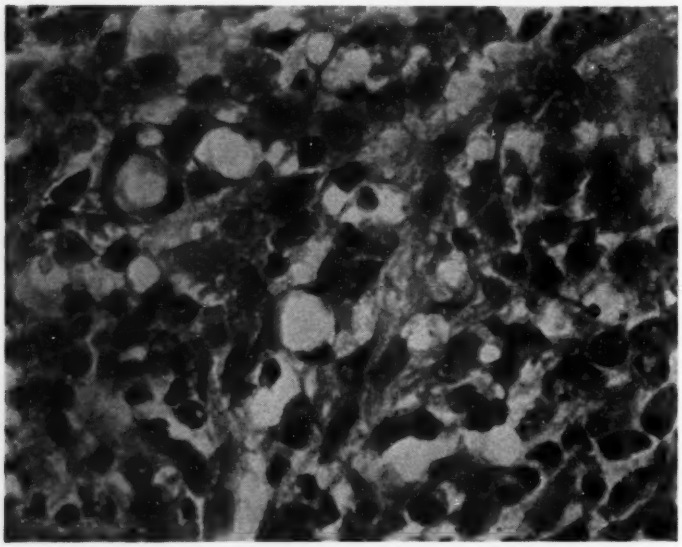

Fig. 5.—Photomicrograph of a section of round-cell sarcoma showing edema and degeneration and slight cellular infiltration with inflammatory cells. (×900. Reduced one-fourth.)

Fallopian tubes showed that the papillary folds were increased in size due to a marked edema, congestion of the vessels, and a diffuse cellular infiltration with lymphocytes, plasma cells, and numerous polymorphonuclear leukocytes. The subjacent muscular coat was also diffusely and intensely infiltrated with inflammatory cells and showed considerable

edema and congestion of the vessels. Sections of the ovaries showed the tunica was thickened due to edema and a cellular infiltration with inflammatory cells. The cortex also showed edema, congestion of the vessels, and diffuse infiltration with lymphocytes, plasma cells, and polymorphonuclear leukocytes, and a moderate number of eosinophils. Several organizing corpora albicantia were found and there were several walls of simple follicular cysts encountered.

Diagnosis.—Round-cell sarcoma of the uterus, showing edema and acute inflammatory reaction; cervicitis, acute and subacute; perioophoritis and oophoritis, acute and subacute; salpingitis, subacute and acute, bilateral; appendicitis, subacute.

Note.—No evidence of a primary undifferentiated carcinoma of the cervix could be found in the sections examined.

The patient had an uneventful convalescence and was discharged from the hospital Dec. 13, 1950, on the ninth postoperative day. Six months following surgery she had gained 18 pounds and was feeling fine. The patient has since moved to another state and further contact is not possible.

Comment

Uterine sarcomas may remain quiescent, growing very slowly over a long period and then rapidly developing. They may subsequently produce widespread local extensions of growth, pushing toward the peritoneum and into the parametric tissues, also becoming submucous and distending the cavity of the uterus. In the latter case, the uterus may express portions of the growth through the cervical canal in the form of polyps. This is unquestionably what happened in this case. True metastases in glands and distant organs may occur, but this manifestation of malignancy occurs later with sarcoma than with carcinoma. Most recurrences are local and regional; secondary deposits are relatively uncommon, so that if the local growth can be completely removed, the prospect of cure is better than it is in cases of epithelioma and adenocarcinoma.

Unfortunately, there is no characteristic symptomatology of sarcoma of the uterus. It must be remembered that sarcoma of the uterus arises most frequently in a pre-existing myoma; therefore, an altered menstruation, abdominal tumor, and the usual symptoms of a fibroid uterus will be the most common complaints found in a statistical study. However, certain symptoms may suggest sarcomatous changes. An abnormal vaginal discharge, first serosanguineous, that later may become foul. The rapid growth of supposedly benign leiomyomas, particularly after the menopause, always suggests the possibility of sarcoma. Pain is frequently associated with tumors of this type. However, as in cancer of the ovary, the majority of cases of sarcoma of the uterus will be diagnosed only at the time of operation, if the possibility is considered. A few may be detected by curettement, but the majority by the gross and histologic examination of the tumor.

It is generally felt that when the diagnosis of sarcoma of the uterus is made, total hysterectomy with removal of the adnexa should be done. There is considerable dispute as to the value of radiation therapy. At the Lahey Clinic no radiation was used in the treatment of sarcoma of the uterus in a report of 75 cases between 1928 and 1946. Of 43 patients operated on by them prior to 1942, 12 were without evidence of disease for periods of from 5 to 15 years. This is a 5 year survival rate of 28.5 per cent of the 43 cases.

In Novak's series of 59 cases, the end results were available in 50 cases. Of these, 15 patients, or 30 per cent, were without evidence of recurrence at the end of 5 years. This had dropped to 12, or 24 per cent, at the end of 10 years. Novak emphasized the point that the outlook for patients with sarcoma of the uterus arising in myomas is relatively good. The mural and endometrial varieties are much less favorable.

The average age in the series of 42 cases recorded by McFarlane of Montreal General Hospital was 50.9 years, the youngest being 22 and the eldest 74 years of age. The largest group, 12 cases, 28.6 per cent, occurred in the fifth decade while 76.2 per cent of the entire number were between 40 and 70 years of age.

Summary

1. A case of round-cell sarcoma of the uterus with good operative results is reported.

2. Round-cell sarcoma of the uterus is reported to occur in 40 per cent of the sarcoma of the uterus group. This entire group constitutes about 4.5 per cent of the uterine malignancies exclusive of chorionepithelioma, which makes it a very rare occurrence.

3. The diagnosis of sarcoma of the uterus is seldom made before operation. However, it should be considered when large myomas are found associated with symptoms of hemorrhage, pain, serosanguineous or foul discharge, cachexia, anemia, and loss of weight.

4. Surgical treatment with complete removal of the uterus and cervix, adnexa, and other structures as indicated is the accepted form of management.

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Department of Case Reports New Instruments, Etc.

CARCINOSARCOMA OF THE UTERUS

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TUMORS, other than teratomas and embryonal tumors of infancy and childhood, showing a combination of malignant epithelial and connective tissue components are rare. Authorities, notably Willis,[10] doubt the validity of many reported, especially in regard to mixed tumors where the sarcomatous element is a spindle-cell type, since malignant epithelial cells not infrequently can be shown to take this form. Saphir and Vass[9] have reviewed one hundred fifty-three so-called carcinosarcomas reported in the literature and consider that possibly only three or four of them may be designated as true carcinosarcomas. The development in successive transplantation of sarcomatous change in the stroma of induced carcinomas of animals is well authenticated (Harvey and Hamilton[2]). The tumor of the uterus which is described here is worthy of record because of the undoubted finding of both well-differentiated papillary carcinoma and well-differentiated rhabdomyosarcoma.

Clinical Notes

The patient, a white woman, age 60 years, para iii, had vaginal spotting over a period of three months. Examination disclosed an enlarged uterus and curettage produced a bulky specimen almost wholly consisting of papillary adenocarcinoma but also (on re-examination) containing large granular and eosinophilic cells. An abdominal hysterectomy was performed after preoperative intrauterine radium to a dose of 6,000 mg. hr. This was followed by postoperative radiation to the pelvis and later vaginal radium (2,000 mg. hr). The patient has been in good health over the twelve months which have elapsed since the operation.

Pathological Specimen

The uterus is illustrated in scale diagram (Fig. 1).

A, the myometrium, showed no evidence of tumor invasion except at G.

B was a well-circumscribed leiomyoma which was firm, and, on section, revealed the typical whorled appearance. Microscopically, there was an excessive fibrohyaline stroma breaking up the smooth muscle bundles.

D was a pedunculated tumor with the pedicle in the left posterolateral wall. It was rubbery in consistency and a uniform glistening white on section, except for the surface. Here there was a mammillated yellowish rind, *E*. No trabeculation could be made out on the cut surface. Microscopic examination of *D* revealed a remarkably uniform picture of large tumor cells, with a fine, almost pericellular, fibrillar connective tissue stroma (Fig. 4). Intimately associated with the stroma there were small connective tissue cells which consisted of little more than a bare spindle or lunate nucleus (Fig. 6). Blood vessels were well formed. The tumor cells were large and had abundant eosinophilic and granular stroma. High-power examination revealed the granular cytoplasm to be a tangle of myofibrils (Fig. 5) which show all stages of differentiation up to a well-organized pattern of skeletal muscle fibers (Fig. 6). The myofibrils were frequently condensed in a central mass leaving a

peripheral zone of paler-staining hyaline or finely vacuolated cytoplasm. Straplike cells, so typical of rhabdomyosarcoma, were also present but were scanty. The nuclei were mainly uniform in structure. They were relatively small and vesicular, often with a prominent nucleolus. While most cells had one nucleus, binucleate and multinucleate forms were present. Bizarre pyknotic nuclei were present in degenerate cells. Mitotic figures were very scanty. The tumor was thus an unusually well-differentiated and slow-growing rhabdomyosarcoma.

The junction, *C*, between leiomyoma and rhabdomyosarcoma was sharp although fine strands of smooth muscle streamed for a short distance into the rhabdomyosarcoma.

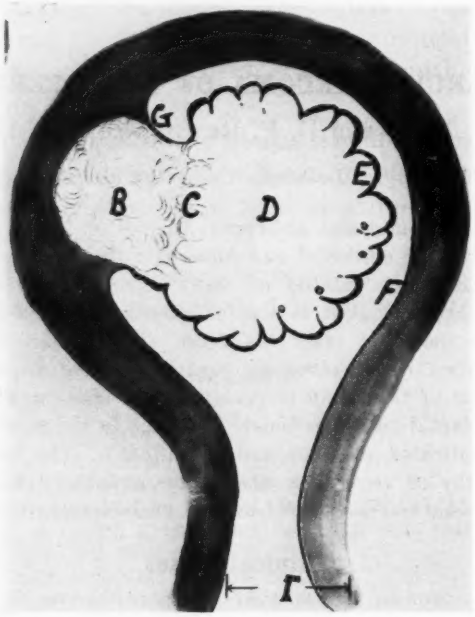

Fig. 1.—Scale diagram of section of uterus, almost coronal.

The yellowish surface rind, *E*, was seen to be composed of relatively well-differentiated papillary carcinoma, consisting of roughly cuboidal cells, one to three cells thick (Figs. 2 and 3). The tumor acini were in places separated from the rhabdomyosarcoma by a well-defined lamina propria (Fig. 3). While roughly uniform in shape, the nuclei were relatively large and hyperchromatic and there was considerable pleomorphism up to bizarre giant nuclei. Mitotic figures were numerous. The papillary tumor penetrated only for a few millimeters into the rhabomyomatous tumor apart from an occasional deeper crypt up to 1 cm. in depth. The round cells seen in the stroma were mainly plasma cells. At the angles of the pedicle of the tumor, *G*, there was invasion of the myometrium by adenocarcinoma to a depth of 0.5 cm. The tumor was more pleomorphic than elsewhere and while in some places there was interstitial permeation by pure carcinoma, in other areas the carcinoma lay in an atypical spindle-cell stroma with little or no evidence of rhabdomyomatous differentiation.

The endometrium, *F*, was atrophic, consisting of little more than a single sheet of flattened epithelial cells with occasional small glandular processes abutting on the myometrium. The latter showed dedifferentiation in the form of relatively large cells, increase of the nucleus to cytoplasm ratio, and occasional bizarre nuclei. These foci represented multifocal incipient carcinoma.

Comment.—We had thus a polypoid uterine tumor which consisted of well-differentiated rhabdomyosarcoma covered with a thin surface rind of undoubted papillary adenocarcinoma. Furthermore, the otherwise atrophic endometrial lining showed multicentric foci of incipient carcinoma but there was no association with rhabdomyosarcoma except in the polypoid tumor. In addition, the complex polypoid tumor abutted on a well-differentiated, largely hyalinized

leiomyoma. Histological distinction between the three neoplastic elements (leiomyoma, rhabdomyosarcoma, and papillary adenocarcinoma) was sharp. Nicholson[7] has given a detailed account of a similar tumor complex in the uterus. There was a leiomyoma present although it was closely associated with the mixed tumor. The rhabdomyomatous element was inconspicuous compared with the carcinomatous element, in contrast to the reverse in our specimen, and in addition myofibrils were not well differentiated. There was also cartilage in his specimen. As in our specimen there was multicentric early carcinoma of the remainder of the atrophic endometrium but we did not find associated sarcomatous elements as Nicholson did. In addition Nicholson's tumor metastasized, reproducing the complex

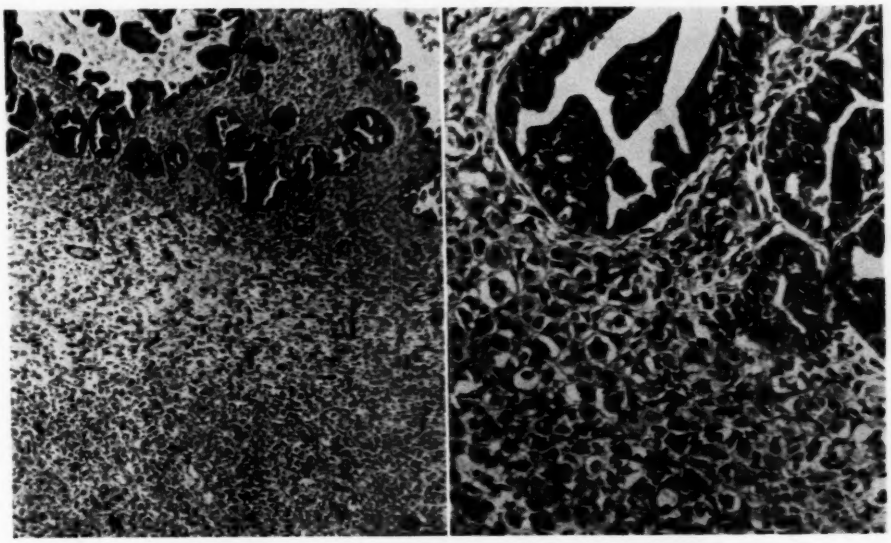

Fig. 2. Fig. 3.

Figs. 2 and 3.—Show papillary adenocarcinoma on the surface of the rhabdomyosarcoma. (Hemalum and eosin stain. Fig. 2 ×40, Fig. 3 ×100.)

features of the primary growth. Saphir and Vass[9] have cast doubt on the validity of all cases in a survey of thirty-six descriptions of carcinosarcomas of the uterus. They missed some important papers including Nicholson's. Nicholson summarized seven cases of uterine tumors of obviously mixed mesenchymatous origin. They were mostly polypoid tumors; one included a carcinomatous element; in one, Hunzicker's case, "the tumour is completely covered by uterine mucous membrane, which shows extensive metaplasia into thick layers of typical squamous epithelium with numerous mitoses, but without keratinization," while in Gebhard's case "there were present uterine glands and squamous epithelium with cell-nests, which presented no signs of carcinomatous proliferation." There is a further account of rhabdomyosarcoma of the uterus, some with other mesodermal elements, by Glynn and Bell.[1] The description covers seventeen undoubted cases and three probable cases and includes two of the cases reviewed by Nicholson. Of those, four tumors, additional to the cases covered by Nicholson, had glandular elements in the tumor complex. More recently Kulka and Douglas[4] have described a polypoid rhabdomyosarcoma of the uterus associated with a carcinoma of the cervix and Poole[8] has described a rhabdomyosarcoma of the uterus intimately associated with undoubted adenocarcinoma.

Saphir and Vass in their review of carcinosarcomas have followed the usual practice of not making a distinction between epithelium of ectodermal and entodermal origin, on one hand, the true epithelium or rind (lepidic) epithelium, and, on the other hand, epithelium of mesodermal origin, the pulp (hylic) epithelium. It should be pointed out that if carcinosarcoma should be applied only where the carcinomatous component arose from rind epithe-

lium, then carcinosarcoma would indeed be exceedingly rare. Following this argument our tumor would be classified only as a mixed mesodermal tumor. This would fall into line with the embryonal classification of tumors by Adami[3]; since the rhabdomyosarcoma would be regarded as a mesothelial hyloma and the carcinomatous component, a transitional lepidoma of mesothelial origin; thus the tumor would be regarded as a mixed mesothelial tumor, or mixed mesodermal, taking the mesothelium as a component of the mesoderm.

We can summarize the foregoing by stating that, though rhabdomyosarcomas are relatively rare tumors, the uterus is a not uncommon site. Though sometimes encountered in a pure form in the uterus, the rhabdomyomatous element is not uncommonly part of a mixed mesodermal tumor (mesothelial in the sense of Adami) in which other elements such as cartilage are identified. In addition the association with carcinoma is too frequent to be coincidental, and is not unexpected, since the epithelial component of the uterus is also mesodermal in origin.

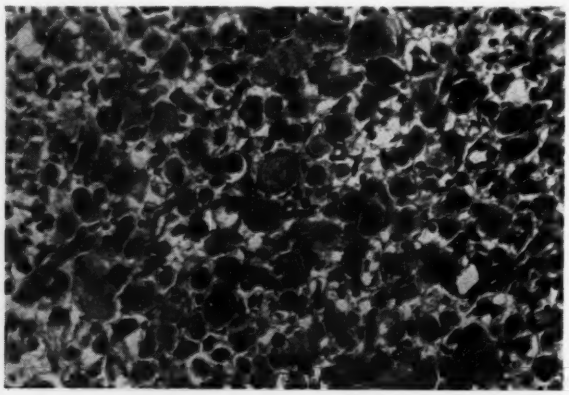

Fig. 4.—Illustrates the rhabdomyosarcoma. Note that many cells have a dark granular center and a clearer periphery. (Modified Mallory stain. ×150. Reduced one-fourth.)

The histogenesis of this type of tumor has been discussed in great detail by Nicholson. He rejects the theory, based on Wilms, that the tumors arise from embryonic rests of mesoderm carried into the area by the downgrowth of the Wolffian duct and considers that such tumors can be explained "on the assumption of a process of dedifferentiation and rejuvenescence of the stroma of the uterine mucosa. It is analagous to metaplasia of epithelium and to heterotopical bone-formation." Willis[10] also concurs with his views (p. 756) and has given a detailed account of metaplasia elsewhere.[11] With the evidence we have available the multicentric carcinoma of the uterine lining indicates a generalized neoplastic trait in the lining epithelium which is against the implication of any embryonic rest, and at the edge of the main tumor the pleomorphic spindle-cell stroma offers some support for the opinion that the rhabdomyomatous element arises from metaplasia of the stroma, while there certainly is no evidence, as there is in a Wilms tumor, of transition between epithelial and connective-tissue elements, since there was always sharp distinction between epithelium and stroma. Accordingly the tumors appear to have arisen from relatively independent cell lines and the appearance offers nothing against Nicholson's views. A number of reviews of the subject contain further speculation in relation to the origin of those tumors. Recognizing (1) the metaplastic potentialities of tissues, (2) the well-substantiated fact, stemming from the work of MacKenzie and Rous,[5] that tissues can be endowed experimentally with a neoplastic trait which can remain latent and be called forth by a wide variety of nonspecific stimuli, and (3) that the epithelium and connective tissue of the uterus share a common embryological origin and presumably a common response to certain stimuli, the occurrence of such complex tumors in the uterus, although remarkable, is quite within the ordinary potentiality of tissue without invoking the presence of embryonic rests to account for them. The complexity of the issues involved obviously precludes too much speculation from histological

observations. It thus appears to us that Nicholson's classical account has carried argument as to the origin of those tumors as far as the evidence from present histological methods will allow. At the same time we have to recognize, since the uterus is by far the commonest site of malignant mixed mesodermal tumors, that the uterine tissues are endowed with a special plasticity the nature of which will remain obscure until, as Nicholson states, "the cause of neoplasia in general shall be discovered, that of this metamorphosis will remain quite unknown."

Fig. 5.

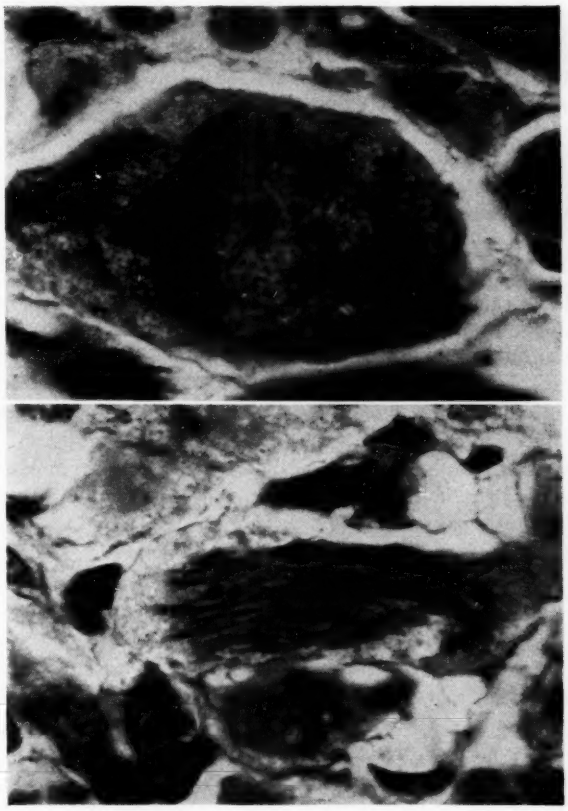

Fig. 6.

Fig. 5.—Shows that the granularity of the cytoplasm is produced by a tangle of myofibrils. Note the prominent nucleolus; the nucleus is not in focus. (Modified Mallory stain. ×1,000. Reduced one-fourth.)

Fig. 6.—Shows well-differentiated myofibrils. (Modified Mallory stain. ×1,000. Reduced one-fourth.)

In respect to the associated leiomyoma, Meikle,[6] in a review of mixed mesodermal tumors of the uterus, claims that associated leiomyomas are probably not fortuitous since they have been present in four cases, or 6.2 per cent, of reported mixed mesodermal tumors. The figures quoted do not appear to be statistically significant.

Summary

A polypoid tumor of the body of the uterus is described in a woman of 60 years. The tumor consisted of well-differentiated rhabdomyosarcoma with a covering rind of papillary adenocarcinoma. The base of the tumor merged with a hyalinized leiomyoma. The endometrium was atrophic but also exhibited foci of incipient carcinoma. The tumor, in the usually accepted sense, is a true carcinosarcoma though following the embryonal classification of Adami it would be regarded as a mixed mesothelial tumor. The status of these tumors

can be covered by the following statement: Though rhabdomyosarcomas are relatively rare tumors, the uterus is a not uncommon site. While sometimes encountered in a pure form, the rhabdomyomatous element is not uncommonly part of a mixed mesodermal tumor in which other elements, such as cartilage, are identified. In addition the association with carcinoma is too frequent to be coincidental, and is not unexpected since the epithelial component of the uterus is also mesodermal in origin. The theory of an origin from embryonic rests is considered untenable.

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EPIDERMOID CARCINOMA IN CYSTIC TERATOMAS

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THE purpose of this paper is to describe in greater detail the process of epidermoid carcinoma occurring in dermoid cysts. This has been described by Faulkner and Douglass[1] as cystic squamous carcinoma of the ovary, and they note this entity to exist in 1 to 2 per cent of dermoids.

Case reports on this type of material have been notably infrequent. Referring to the literature of the past ten years, we have been unsuccessful in finding significant reports. Our purpose, herewith, is to present two cases of epidermoid carcinoma occurring in dermoid cysts.

The cases herewith presented were gleaned from a review of the solid tumors of the ovary which occurred on the Gynecological Service of the Metropolitan Hospital. The material surveyed was of the ten-year period, June 1, 1943, through May 31, 1952, inclusive. In each of these years, approximately 2,000 cases were admitted. The predominant racial strains were Negro and Puerto Rican. During the survey period 29 cases of cystic teratomas were encountered at surgery. Of these cases there were 5 instances of bilateral dermoids, or a percentage of 17.24. This figure is higher than that noted by Randall and Hall[2] (11.9 per cent), and by Vara and Pankamaa[3] (10.4 per cent), respectively. In our series there were two cases of epidermoid carcinoma, or a 6.9 per cent incidence. It is, of course, obvious that the high percentage of malignancy exhibited in this small group of cases is not a true reflection of their relative occurrence. As noted by many authors malignancy occurring in dermoids is extremely low, although some authors have found difficulty in quoting exact numbers. Thus, Davis noted the occurrence of this entity and is satisfied in saying that it is extremely infrequent. Blackwell and associates[5] noted the occurrence of two cases of epidermoid carcinoma which occurred in 100 cases of cystic teratomas. Novak[6] concurs in the opinion that cancerous changes in dermoids are relatively rare. We concede our unduly high percentage in this series but feel, nonetheless, that, due to the paucity of such reported cases, this report should be of interest.

Case 1.—E. M., No. 152750-45, was a 33-year-old, gravida i, para i, white woman who was admitted to the Metropolitan Hospital on June 27, 1945, with the chief complaints of the presence of a mass in the lower abdomen, abdominal pains, backache, and vaginal bleeding every two weeks. She had observed a mass in the lower abdomen for the preceding two weeks. For the past several months she had experienced daily severe lower abdominal pains and backache which were aggravated by exertional fatigue and at the time of the menses. During the past two years, she had experienced episodes of polymenorrhea with periods every two weeks, lasting 7 days, being rather heavy with passage of clots. Her normal menstrual pattern was menarche at 15 years, periods every thirty days for seven days. Past history and family history were noncontributory. The past systemic history was negative except for an unexplained 25 pound weight loss in the past five years. Physical examination was irrelevant except for the following pertinent findings: abdominal examination revealed an irregular large grapefruit-sized mass filling the lower abdomen. Vaginal examination showed the fundus anterior and of normal size, the cervix was pointed anteriorly, high, and the portio was clean and firm. There was noted a large mass about the size of a four months' gestation which in the main was cystic though exhibiting solid nodular areas and which filled the pelvis. Routine laboratory examinations were within normal range: The Wassermann

test was negative; urinalysis, negative; hemoglobin, 70 per cent; erythrocyte sedimentation rate (Westergren), 5/20. On July 18, 1945, a laparotomy and a left oophorectomy were performed. At this time a large dermoid cyst of the left ovary 15 cm. in diameter, impacted in the pelvis, was found. Adhesions were freed and the ovarian tumor was delivered completely excised without rupture. The right ovary was normal. Microscopic examination of the ovarian cyst showed dermoid characteristics consisting of elements of skin, hair, bone, cartilage, sebaceous and sudoriferous glands. Also, there were islands of epidermoid malignant epithelium invading the ovarian stroma (See Figs. 1, 2, 3, and 5).

The patient passed an uneventful postoperative course. She was discharged from the hospital on Aug. 1, 1945, in satisfactory condition. Follow-up examinations were made at yearly intervals, and at last contact with the patient in 1951, six years postoperatively she was living and well, and working 12 hours per day.

Fig. 1 (Case 1).—Low-power photomicrograph of wall of cystic teratoma showing characteristic stratified squamous epithelium and normal accessory structure. This was representative of the greater portion of this specimen.

CASE 2.—J. B., No. 12893-49, was a 54-year-old gravida i, para i, Negro woman who was admitted to the Metropolitan Hospital on Nov. 11, 1949, with the chief complaints of dull, intermittent right and left lower quadrant pains of three months' duration. She was apparently well until three months prior to admission at which time the onset of the lower quadrant pains occurred. They lasted 30 to 90 seconds and occurred two to three times daily. There was no radiation of pain. The patient had observed, for the past five years, palpable masses in both lower abdominal quadrants. These masses increased in size although symptoms first arose only three months ago. Her normal menstrual pattern was menarche at 14 years, periods every thirty days for five days. The menopause occurred in 1932 when she was 37 years of age. Her past history was negative except for the fact that she had been attending the Cardiac Clinic for the past twelve months and that she had been using digitalis, 0.1 Gm. daily. In so far as family history was concerned, both parents and a sister died of heart disease. Review of the systemic history revealed the following pertinent information: Dyspnea, orthopnea, and cardiac palpitation had been noted for the past five to six years. Intermittent ankle edema had been present. Of particular importance was anorexia accompanied with a 24 pound weight loss in the past four months. The important findings on physical examination were as follows: The blood pressure was 250/136, the heart was enlarged outward and downward with the point of maximal impulse at the sixth intercostal space outside of the midclavicular line. The pulse rate, equal to the ventricular rate, was 132. A systolic thrill was present over the pulmonic and aortic areas. On abdominal

examination, two distinct masses in both lower quadrants, 10 by 8 cm. in size, were palpable. They were mobile, firm, anterior, and close to the midline. On pelvic examination the uterus could not clearly be made out, the cervix was anterior, clean, firm, and nontender. There were masses originating in either adnexal region, and extending to the level of the umbilicus. The left-sided mass was firm, rather mobile and smooth in outline, while the right lower quadrant mass appeared to be fixed.

Fig. 2.

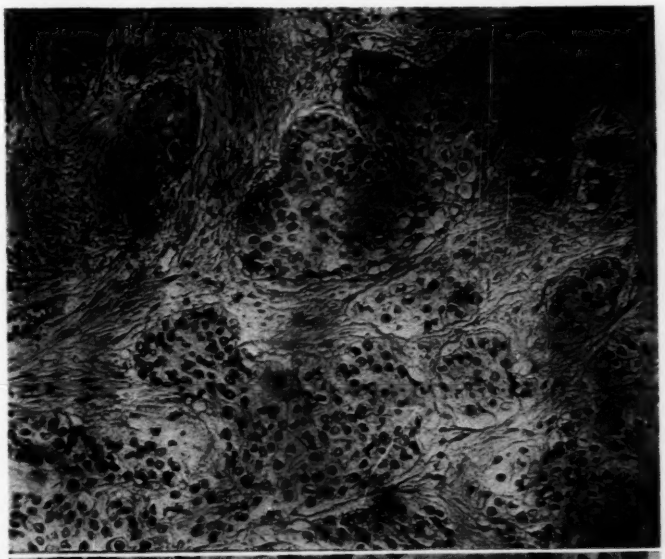

Fig. 3.

Fig. 2 (Case 1).—Low-power photomicrograph. Island of epidermoid carcinoma traversing and invading the subepithelial parenchyma. Nuclear atypia and mitotic figures can readily be seen.

Fig. 3 (Case 1).—High-power photomicrograph. Same area as shown in Fig. 2, showing in more detail the characteristic elements of malignancy. The epidermoid character of the lesion is observable as is the anaplastic character of the cells.

Laboratory Data.—The hemoglobin was 80 per cent, erythrocyte sedimentation rate (Westergren), 35/70. The blood chemistry was normal, the Mazzini test negative. Urinalysis of a catheterized specimen was essentially negative. A scout film of the abdomen showed calcified uterine fibroids. The preoperative diagnoses were: (1) right ovarian malignancy; (2) fibromas of the uterus; (3) hypertensive heart disease with aortic valvular involvement.

On Nov. 18, 1949, a laparotomy was performed at which time the following findings were noted when the peritoneal cavity was entered. The uterus was about 12 cm. in size with a

9.0 cm. calcified, subserous fibroid arising from the anterior uterine wall; there was a 10.0 cm. cystic, mobile ovarian mass on the left; from the right adnexal region there arose a large ovarian tumor extending to the umbilicus to which loops of small intestine were adherent.

Fig. 4.

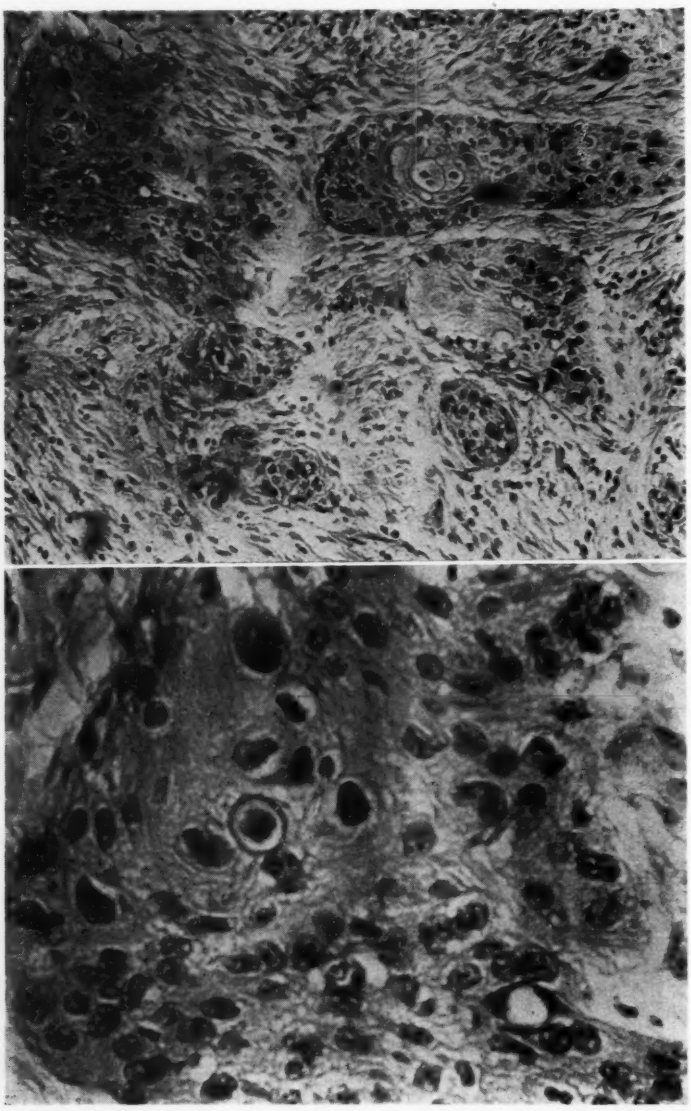

Fig. 5.

Fig. 4 (Case 2).—As in Fig. 2 this shows similar invasion of the malignant islands of epidermoid carcinoma. The character of the cells appears to be less differentiated to a slight degree than that of the cells noted in Case 1, Fig. 2. What appear to be lighter-staining areas are in all probability acanthomatous.

Fig. 5 (Case 2).—High-power photomicrograph of areas previously noted in Fig. 4, showing characteristic nuclear changes of malignancy and the occurrence of several large differentiated atypical cells. Note the relatively loose, uninvolved stromatogenous structures.

On separation of the small intestines from the tumor wall, the tumor mass suffered a rent through which escaped an odorless, thick, yellowish fluid containing hair. Most of this escaped material was evacuated. The total surgical procedure consisted of supracervical hysterectomy and bilateral salpingooophorectomy. Gross pathological examination of the

ovarian specimen showed the presence of bilateral dermoids. Microscopic examination (Fig. 4) revealed cystic teratomas to be present with islands of malignant epidermoid elements invading the ovarian stroma of the right-sided cyst.

The patient's postoperative convalescence was slow and discouraging. On Dec. 30, 1949, she was discharged to our Clinic for deep pelvic x-ray therapy. She was readmitted to our Cancer Hospital Unit on Jan. 9, 1950. Important physical findings on admission were: healed midline abdominal incision, tumefaction in both lower abdominal quadrants, especially on the right. Pelvic examination revealed a cervical stump which was fixed, posterior, smooth, while a large intrapelvic firm, nodular mass extended to the umbilicus with nodules palpated through the right and left forniceal areas. The rectal examination confirmed the pelvic findings. The diagnosis was postoperative metastatic ovarian carcinoma. The patient's active therapy consisted of soft diet, digitalis, multiple vitamins, and analgesics (every four hours). In addition deep x-ray was prescribed for a total of 2,000 r through one anterior field (20 by 20 cm.) at a 50 cm. target distance to be given twice weekly, 100 r per treatment. Filtration was 0.5 mm. Cu and 1.0 mm. Al. However, the patient's poor condition permitted only four treatments continuing until Feb. 1, 1950, for a total dose of 400 r in air. Her condition rapidly deteriorated and she developed progressive heart failure. The abdominal pain became increasingly severe and intolerable. She died on March 27, 1950. On the day prior to her demise, examination revealed evidence of generalized carcinomatosis of the abdomen and supraclavicular nodular involvement. Autopsy consent was refused by her family.

Comment

From the two cases herein reported in detail, and from the pathology observed, certain important features may be noted. It will be observed that the patient who died of diffuse carcinomatosis was subjected to difficult surgery and in all probability incomplete removal of the tumor mass. It was tragic that this tumor exhibited epidermoid carcinoma within the dermoid cyst. This case bears comparison with the first one reported which was pathologically identical, but in which the integrity of the tumor mass was maintained during surgery. A detailed review of the microscopic pathology reveals an amazing identity of pathologic structures (Figs. 1, 2, 3, 4, and 5). On this basis, both patients should have survived. The important difference was the rupture of the tumor mass in the one patient who died.

It has been pointed out by numerous authors that contents of a dermoid cyst are irritating and may give rise to an aseptic peritonitis. Randall and Hall[2] feel that only when tumor contents become necrotic do such irritating factors come into play. However, we feel that, in view of the possibility of cancerous change occurring in a definite percentage of dermoids, an aseptic peritonitis is relatively unimportant. It is emphasized rather that the integrity of the tumor mass must be maintained in order to avoid possible implantation of malignant material.

Summary

Two cases of epidermoid carcinoma in dermoid cysts are reported. One patient operated on in 1945, in which case the cyst was completely removed, was living and well when last checked, six years later. The other patient died only four months following surgery. It is stressed, in view of the similarity of microscopic findings, that the determining factor between survival of the one patient and the death of the other was spillage of malignant cyst contents in the patient who succumbed.

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CHEMICAL PERITONITIS DUE TO DEGENERATED FIBROID

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FIBROIDS of the uterus in pregnancy are not uncommon; the incidence is usually stated as 2 to 5 per cent.[1] One of the most frequent complications is degeneration of the fibroid which occurs in about 20 per cent of cases. When degeneration of the fibroid occurs during pregnancy, opinion is divided as to its management. Treatment varies from conservatism to surgical removal of the fibroid. Approximately 10 per cent of such cases require surgical treatment.

At Cook County Hospital management is conservative with the thought that the fibroid may undergo regression following delivery of the infant. However, degeneration may occur post partum and if conservative management is continued further, complications may arise, including necrosis, liquefaction, and perforation with resulting chemical peritonitis. The literature for the past ten years was reviewed and no cases were found with such extensive complications of a fibroid following parturition. The following case is presented because it demonstrates such an unusual complication.

The patient, a 32-year-old Negro woman, gravida ii, para i, was first seen at the prenatal clinic of Cook County Hospital on Aug. 15, 1951. The expected date of delivery was Jan. 22, 1952. The menstrual history was normal. A previous pregnancy had resulted in a normal spontaneous delivery of a 9 pound infant in 1934. The only other significant fact in her past history was treatment for syphilis in 1950.

General physical examination was essentially negative. Obstetrical examination revealed a uterus which was enlarged to the size of a nine months' gestation, although the period of amenorrhea was only four months. Pelvic examination revealed no abnormalities. The laboratory reported the urine normal and the serologic test positive.

The following week, at her second prenatal visit, a large fibroid was noted which occupied the entire right upper quadrant of the abdomen, extending up to the xiphoid. The patient had no complaints referable to the fibroid. Conservative management was elected. She attended the clinic at regular intervals and continued to be asymptomatic.

On Nov. 25, 1951, the patient entered the hospital and twenty minutes after admission spontaneously delivered a living 4 pound, 4 ounce infant. After delivery of the baby the uterus remained almost the size of a full-term pregnancy and was explored manually. Several submucous and intramural fibroids were palpated, as well as a large firm pedunculated fibroid at the upper aspect of the uterus, the size of a grapefruit. Following delivery of the placenta there was no apparent decrease in the size of the uterus.

The patient was afebrile at delivery but 24 hours later her temperature was 102° F. General physical examination gave no indication of the cause of the patient's fever. The abdominal mass was still firm, nontender, and two fingerbreadths above the level of the umbilicus. Penicillin and sulfadiazine therapy were instituted. By the fifth postpartum day the mass appeared cystic and larger, extending to the xiphoid process. On the tenth postpartum day, in spite of chemoantibiotic therapy, the patient continued to have a septic course, with temperatures ranging to 103° F. A complete blood count was taken and the hemoglobin was 55 per cent, red blood cell count 3.72 million, and white blood cell count 7,450. She was given 500 c.c. of whole blood.

On the eleventh postpartum day an exploratory laparotomy was performed under general anesthesia. When the abdomen was opened, a large, cystic mass was found filling the entire abdominal cavity. Delivery of the mass was difficult because of dense adhesions to the bowel, stomach, and omentum. On freeing of the adhesions a perforation was found with leakage of thick greenish-yellow purulent fluid into the peritoneal cavity. After delivery of the mass out of the abdomen it was found to be a pedunculated, degenerated subserous fibroid. Myomectomy was performed. One million units of aqueous penicillin was instilled into the peritoneal cavity and the abdomen was closed without a drain. The patient received 1,000 c.c. of whole blood during surgery.

For the first 48 hours postoperatively, the patient continued to be febrile, the highest temperature being 102° F. The subsequent postoperative course was uneventful. The patient was discharged on the tenth postoperative day. The baby was discharged from the premature station on Feb. 7, 1952, weighing 5 pounds, 4 ounces.

Summary.—A case is presented of a 32-year-old woman in whom a large asymptomatic fibroid was first discovered when the period of gestation was 18 weeks. Conservative management was elected and delivery of a live baby was uneventful. Early in the puerperium the tumor degenerated, spontaneously perforated, and caused chemical peritonitis. Myomectomy was performed and the patient recovered uneventfully.

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ACUTE PURULENT SALPINGITIS DURING PREGNANCY

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THE occurrence of acute, purulent infection of the Fallopian tube during pregnancy is a rare condition. Most textbooks do not mention the entity, probably because it has been considered impossible for infection to traverse the barrier of cervix, uterus, and tube in the gravid state. Novak[1] believes the pelvic hyperemia in pregnancy to be an effective deterrent to infection. A brief review of two cases follows:

CASE 1.—M. B. (University Hospital, Columbus, Ohio, No. 490694 C), a 19-year-old Negro girl, was admitted to the Gynecologic Service on May 15, 1950, with the chief complaint of severe lower abdominal pain. This pain had begun suddenly six hours previously when she was in bed. She did not faint, but felt as though she were going to faint. She vomited three times following the onset of the pain. The last menstrual period had begun in early March. Her previous record showed numerous visits to the Gynecologic Clinic for treatment of chronic pelvic inflammation. She had had treatment for syphilis. She had been pregnant once before and aborted at five months.

Examination.—The blood pressure was 110/68; temperature 101° F.; pulse 100. There was pronounced tenderness throughout the abdomen, especially in each lower quadrant. No masses were felt; there was no muscle spasm. The cervix appeared bluish and was exquisitely tender when moved. The uterus was the size of a two and a half months' gestation. The adnexa could not be palpated because of tenderness. The cul-de-sac was not full.

Laboratory Data.—The hemoglobin was 11 Gm.; the white blood count 16,100 with 94 per cent polymorphonuclear leukocytes; the sedimentation rate (Westergren) was 43 mm. per hour. The urine had a trace of sugar and many white blood cells. The serologic test for syphilis was positive.

Hospital Course.—The patient was taken to the operating room with a diagnosis of acute pelvic inflammation or ectopic pregnancy. Under anesthesia the cul-de-sac was needled, yielding seropurulent material. The abdomen was then opened. The uterus appeared to contain an early pregnancy. The right tube was swollen and from the fimbriated end exuded yellow, purulent material. Stripping the tube upward yielded more of the same material. The appendix was removed and the abdomen closed. The postoperative course was one of moderate distention treated with the Miller-Abbott tube and suction. The temperature returned to normal slowly under streptomycin therapy. Culture of the purulent material was reported as negative for microorganisms. The patient aborted three weeks postoperatively. She was next seen with her third pregnancy and was delivered uneventfully at term on June 10, 1951.

CASE 2.—D. F. (Bethesda Hospital, Cincinnati, Ohio, No. 250541), a 23-year-old white woman, was admitted to the hospital Jan. 8, 1952, complaining of lower abdominal pain. This pain began suddenly the morning of admission and continued. Vaginal bleeding began eight hours after the onset of pain and continued in slight amount. Chills and fever were present. Vomiting occurred once following the onset of pain. Her last menstrual period occurred October 28 and she had had the usual signs and symptoms of pregnancy. Her first pregnancy, four years earlier, terminated in a normal delivery; a second pregnancy, two years earlier, ended in delivery of a stillborn infant with numerous anomalies incompatible with life.

Examination.—The temperature was 102° F., blood pressure 112/68.

The abdomen was tender over the lower half. There was neither rigidity nor rebound tenderness. No masses were felt. On bimanual examination the uterus was consistent with an early pregnancy, but was quite tender, as were both adnexa.

Laboratory Data.—White blood cells 27,000 with 90 per cent polymorphonuclear cells. The hemoglobin was 12 Gm.; urine, negative.

Hospital Course.—Following consultation, the diagnosis of appendicitis or ectopic pregnancy was made and laparotomy was advised. Upon opening the abdomen the pelvis was found to be bathed in thick, yellow, creamy, odorless pus. Attention was first turned to the appendix, but this was completely normal. Investigation of the reproductive system showed this same pus to be pouring from the fimbriated ends of both tubes, although the tubes themselves showed very little evidence of inflammation. The uterus was consistent with early pregnancy. The ovaries were normal. The pus was cultured and the abdomen closed. The postoperative course was uneventful. There was no distention or ileus at any time, despite the large amount of pus in the pelvis and abdomen. Spontaneous, apparently complete abortion occurred on the second postoperative day. The temperature was normal on the first postoperative day and remained so for the remainder of her stay in the hospital. She was discharged on the tenth postoperative day. The culture of the material obtained at laparotomy was reported as *Staphylococcus albus.*

Comment.—The literature on this subject was reviewed by G. Gordon Lennon in 1949[2] when he reported two cases. All previous references were in the French literature. Preoperative diagnoses were usually ectopic pregnancy or appendicitis, both of which were considered in our cases. Abortion occurred in the cases reported here as in those reported by Lennon. It is possible that the condition is more common and that cases seen after abortion are then diagnosed as infected abortions. If this were the case it would be evident that the cause of the disruption of the pregnancy was the infection, not the laparotomy. Exploratory laparotomy should not cause abortion routinely.

The etiology of the infection may be obscure. In the first case presented here there had been pelvic infection for many years, and the infection during pregnancy was probably a flare-up of the old focus. However, the second patient had never had any previously known infection. She had desired this pregnancy very much, and instrumentation for induction of abortion was very unlikely.

It is probable that this condition is more common than one would assume from the lack of mention in the American literature, since many physicians recall having seen one or more similar cases. It is therefore one of the possible entities to be considered with abdominal pain in early pregnancy.

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PREGNANCY COMPLICATED BY SEVERE MEGALOBLASTIC ANEMIA AND LEFT VENTRICULAR HEART FAILURE

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WHILE uncommon in the countries of the temperate zone, megaloblastic anemia of pregnancy is not so uncommon in the tropics.

Prior to the use of blood transfusions, liver therapy, and more recently folic acid, the prognosis was grave. Maternal mortality was as high as 42 per cent and a stillbirth rate of 53 per cent was reported.[1] Now, however, if the disease is recognized, and proper treatment is instituted, the prognosis is not so grave. In India, this condition is still high on the list of causes of maternal mortality.[11]

The etiology of this condition is still obscure but many investigators attribute it to a nutritional deficiency. It has been found that the incidence of this anemia is high in the poor and the middle class, where the diet is deficient in total protein and animal protein.[10, 11] However, this condition has been present in women for whom the diet was thought to be adequate. Since the discovery that folic acid, when administered, produces normal hematopoiesis,[3] it has been felt that this may be the deficient substance,[7] but not all cases have responded to folic acid.[11]

Other theories advanced are:

1. With the temporary impairment of the secretion of hydrochloric acid in a considerable proportion of pregnant women, a similar disturbance of the intrinsic factor may occur and this, plus a strain such as twins, toxemia, sepsis, hemorrhage, or other factors, would precipitate the anemia.[2, 4]

2. Absorption from the gastrointestinal tract is impaired due to an altered hydrogen ion concentration secondary to reduced gastric acidity.[2]

3. An endocrine factor may be the inhibiting influence but the exact nature is obscure.[4, 7]

Megaloblastic anemia may develop at any time during the childbearing period. It is seen more often in the multipara and recurrence with succeeding pregnancies may occur. Most often the onset is noted during the third trimester of the pregnancy or in the puerperium and it may be rapid or insidious.

The signs, symptoms, and physical findings noted are: marked pallor with a pearly-white appearance of the skin, weakness, dyspnea, edema, purpura in some cases, and, in 40 to 50 per cent of the cases, gastrointestinal complaints namely (vomiting and diarrhea). Pyrexia may be present but its association with sepsis is not frequent. Hemic murmurs, splenomegaly, hepatomegaly, and retinal hemorrhages may be found on examination. Neurologic disorders do not occur.[4, 7, 8, 10]

The peripheral blood picture reveals an anemia of variable severity and a color index which may range from above to below normal. There is a low hematocrit. Leukopenia is common with the granular cells principally affected. The reticulocyte count is low.[4, 8]

The findings in bone marrow studies are constant and therefore diagnostic.[2, 4] The marrow reveals a mixed megaloblastic and normoblastic reaction with formation of clumps of deeply basophilic promegaloblasts and megaloblasts.

Achlorhydria is not the rule in these cases.

Spontaneous recovery after delivery is known to occur.

The treatment is blood transfusion if necessary, folic acid parenterally or orally, liver, a diet rich in protein, vitamins, and minerals, and iron if the hemoglobin concentration is low.[6-12] Within 6 weeks following delivery the blood picture usually returns to normal and during this period the patient should receive folic acid.

Folic acid used as a prophylactic measure should be given in the last trimester of pregnancy and a dose of 2 mg. daily is recommended.[10]

Case Report

Mrs. M. N., No. 13538, a 28-year-old white married, gravida iii, para ii, whose last normal menstrual period was Nov. 8, 1949, and whose expected date of confinement was Aug. 15, 1950, was admitted to the obstetrical ward on June 19, 1950. The chief complaints were pallor, weakness, swelling of the ankles, and a nonproductive cough, all of one week's duration. The patient also noted that the abdomen was not increasing in size. There was no history of bleeding.

The patient was first seen in the Prenatal Clinic on April 11, 1950, at which time her general condition was good. Her weight was 98½ pounds, the blood pressure was 98/54, and the uterus was the size of a 4 months' gestation. She was last seen in the clinic 2 weeks prior to admission, at which time she had no complaints and no abnormal findings were noted. The blood pressure was unchanged and the patient's weight was 104½ pounds.

Menstrual History.—Menarche was at the age of 16 years, with a cycle of 28 to 35 days, duration of 4 days, normal flow, no dysmenorrhea.

Obstetrical History.—In 1945 the patient had a normal spontaneous delivery of a 6 pound, 1 ounce, living child. However, she ran a morbid course and the hemoglobin dropped from 10.8 Gm. (74 per cent) with a red blood count of 3.7 million to 5 Gm. (34 per cent) with a red blood count of 1.82 million. There was no abnormal blood loss. No cause for the morbidity was found. The patient was treated with blood transfusion and sulfathiazole and was discharged on the twenty-second postpartum day. The hemoglobin and red blood count were normal.

On Oct. 27, 1946, the patient had a spontaneous delivery of a living premature male child (4 pounds, 3 ounces) after an ovarian cyst, which had obstructed the birth canal, was dislodged from the cul-de-sac. The hemoglobin was 7.5 Gm. (52 per cent) and the red blood count 3.1 million. She was discharged on the fifth postpartum day. She had had no prenatal care.

Surgery.—On Nov. 18, 1946, a right salpingo-oophorectomy with removal of a pseudomucinous cystadenoma 13 cm. in diameter was performed. The hemoglobin was 7 Gm. (48 per cent) and the red blood count 3.5 million.

She was given a blood transfusion and was discharged on the eighth postoperative day with normal blood count.

Physical Examination.—The temperature was 98° F., pulse 110, blood pressure 150/80.

The patient was a small, thin woman who appeared acutely and critically ill with marked pallor, dyspnea, and orthopnea.

There was marked pallor of the mucous membranes and edema of the face. There was dullness at the bases of both lungs and râles throughout both lung fields posteriorly. The heart was enlarged; the apex was at the anterior axillary line; there was regular sinus tachycardia and rough apical systolic murmur, no thrill. The breasts were negative. The abdomen was gravid with a well-healed lower abdominal midline scar. The fundus was at the level of the umbilicus. The fetal heart was not heard but the patient stated that fetal action was present. The liver edge was felt two finger breadths below the costal margin and was tender. There was 4 plus presacral pitting edema of the back and 4 plus pitting edema of the extremities. The skin had a pearly-white pallor.

The impression was: (1) intrauterine gestation of 6 months; (2) severe anemia, type to be determined; (3) acute left ventricular failure; etiology, severe anemia.

The medical department was consulted. The findings and diagnosis were confirmed, and the following treatment was instituted: The patient was placed in an oxygen tent and digitalized with 0.5 mg. ouabain intravenously and then 0.2 mg. digitoxin daily. Mercuhydrin, 2 c.c. and then 1 c.c. intramuscularly, was given daily. A sternal marrow puncture was performed and a transfusion of 1,000 c.c. of whole blood was slowly administered. Liver

extract, 1 c.c. daily, Mol-Iron, 2 tablets three times a day, large doses of vitamins, folic acid, 50 mg. intramuscularly daily, and penicillin, 600,000 units daily intramuscularly, were given.

Laboratory examination showed: hemoglobin 13 per cent; red blood count 680,000; color index 1.08; white blood count 25,300; polymorphonuclear leukocytes 64; nonsegmented cells 5; lymphocytes 30; blasts 3, monocytes 1, platelets 80,000. A smear revealed achromia and macrocytosis.

The sternal marrow showed prominent megaloblastic hyperplasia associated with marked anisopoikilocytosis, polychromasia, and slight macrocytosis of the erythrocytes. *Diagnosis:* Megaloblastic anemia.

Other laboratory findings were: urea 65 mg. per cent; creatinine 1.3 mg. per cent; carbon dioxide combining power 43 volumes per cent. Urine: specific gravity 1.018, albumin, trace; sugar, negative, microscopic examination, negative. The Wassermann test was negative. The blood was type O, Rh positive.

The patient, following the blood transfusion, appeared much better and improvement in her general condition was noted daily. On June 25, the sixth hospital day, the oxygen tent was no longer necessary. The fetal heart beat was now heard. Her blood count showed a 55 per cent hemoglobin and a red blood count of 2.85 million, hematocrit of 35; white blood count 30,000. Digitalis and Mercuhydrin were discontinued on the ninth hospital day. The hemoglobin was 62 per cent, red blood count 3.14, color index 1, platelets 208,000, reticulocytes 7.8 per cent. Bleeding and clotting times were normal. The total plasma proteins were low. On the twentieth hospital day the hemoglobin was 66 per cent, red blood count 3.2 million, white blood count normal. The parenteral folic acid was discontinued and the patient received 10 mg. folic acid three times daily. On July 18, the thirtieth hospital day, the patient was discharged to the outpatient department with a hemoglobin of 82 per cent and a hematocrit of 45. The uterus was the size of a 7½ to 8 months' gestation. Folic acid, 10 mg. three times a day, was continued.

On July 31 the patient was readmitted because of slight painless vaginal bleeding. The blood pressure was 140/80, the lungs were clear, the heart was negative. The uterus was the size of an 8 months' gestation, with vertex presentation. The fetal heart rate was regular. There was slight uterine tenderness in the left lower quadrant. No active vaginal bleeding was present. From soft tissue studies, it appeared that the placenta was on the posterosuperior wall of the uterus. While under observation the patient had slight painless vaginal bleeding. The hemoglobin was 10½ Gm. (74 per cent), the red blood count 2.49 million, the white blood count 7,200, the hematocrit 44. On August 5, the patient signed out of the hospital at her own risk. On August 11, she was readmitted with the cervix fully dilated and a history of being in active labor for four hours, and was delivered spontaneously of a living female child weighing 5 pounds, 1 ounce, from the occiput posterior position. Anesthesia was pudendal block with ½ per cent procaine. A right mediolateral episiotomy was performed. The placenta showed evidence of a small area of premature separation. The patient was discharged on the sixth postpartum day, with hemoglobin 12 Gm. (85 per cent) and hematocrit 44. She was continued on folic acid for 6 weeks and subsequent follow-up revealed no evidence of anemia in the mother or child.

Summary

A severe case of megaloblastic anemia of pregnancy is presented. The satisfactory therapeutic response of the patient to folic acid therapy is noted.

I wish to express my appreciation to Dr. William C. Meagher Director of Obstetrics and Gynecology, for his advice and suggestions in the preparation of this report.

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RUPTURE OF AN ANEURYSM OF THE LEFT RENAL ARTERY DURING PREGNANCY

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IT IS fitting that this complication of pregnancy be reported inasmuch as such a combination of factors does not often present itself.

Intraperitoneal hemorrhage has an abrupt onset and the symptoms as well as the findings are definite and clear-cut. It is an entity which demands immediate treatment. Retroperitoneal hemorrhage does not present as definite a picture and there may be a lag between the onset of the bleeding and the final hemorrhage. During this interval the patient clinically may improve; then the second hemorrhage may occur. This grace period may vary from a few hours to two weeks. The final episode of bleeding is more severe and must be controlled.

Retroperitoneal hemorrhage has various causes. Rupture of the spleen, according to Eastman,[1] is a rare complication of gestation. Burnett and McMenemey found only 15 cases in the literature up to 1930.

Rupture of the uterus may occur and the hemorrhage remain retroperitoneal. Such a case is included in the series reported by Gordon and Rosenthal.[2] In this instance the retroperitoneal hemorrhage which consisted of free and clotted blood was in the right retroperitoneal space behind the cecum.

Hemorrhage from ruptured uterovarian veins during pregnancy must be considered. Such hemorrhage may be intra-abdominal, retroperitoneal, or a combination of these two types. Confined retroperitoneal bleeding is usually associated with unilateral abdominal and back pain. Rupture of the veins located between the folds of the broad ligament and in the areolar tissue of the posterior retroperitoneal space has, as in the case being reported, resulted in enormous hematomas extending from the thoracic to the pelvic diaphragms. Treatment, if effective, must be aggressively initiated. Seventy-five cases have been reported in the literature to May of 1950.[3] Rupture has occurred as early as ten weeks' gestation and as late as 21 days post partum.

Small and Johnson[4] report a retroperitoneal hemorrhage which occurred in a 34-year-old Mexican woman, a gravida ix, para viii. Her first pain occurred on the morning of the first postpartum day; then, after an interval of 36 hours, she was found in deep shock. The hemorrhage was controlled by ligation of the inferior vena cava, several right lumbar veins, and the right sympathetic chain, after supravaginal hysterectomy and right nephrectomy. The source of the bleeding was not stated.

A ruptured aneurysm occurring in pregnancy may result in a retroperitoneal hemorrhage, and the splenic artery is most often involved. Gillam's[5] case reported in 1941 is that of a spontaneous rupture of the splenic artery in the eighth month of a first pregnancy in a 26-year-old Belgian woman. The interval between the first and second hemorrhage was approximately two weeks. The first hemorrhage was limited to the lesser sac. She was successfully handled by splenectomy at the time of the second hemorrhage.

Danforth[6] reported a case of rupture of the splenic artery in a 28-year-old gravida iii at the end of the seventh month of pregnancy. He suggests active therapy to consist of either removal of the aneurysm with excision of the spleen as well, if necessary, or the ligation of the splenic artery. The latter procedure will carry with it an aseptic necrosis of the spleen which does no harm.

Cosgrove, Watts, and Kaump[7] reviewed rupture of splenic arterial aneurysms. Fifteen patients were pregnant; the period of gestation ranged from four months to the puerperium, and the rupture was fatal in 14 of the 15 cases. In 8 of the 15 cases the pathogenesis was congenital. Arteriosclerosis was not considered a factor in any of the 15 patients who were pregnant.

Tennant and Starritt's[8] case was a rupture of the splenic aneurysm occurring spontaneously in a 36-year-old gravida ix. Autopsy revealed three congenital aneurysms, one of which ruptured. They state that the main hope of salvaging the occasional patient lies in adequate supportive therapy with rapid control of the bleeding. They are of the opinion that the latter is best accomplished by simple ligation of the splenic artery near the proximal end, the spleen being left to undergo aseptic atrophy.

Priddle's[9] case is that of a spontaneous rupture of a congenital aneurysm of the left external iliac artery in a 29-year-old Negro woman, gravida vi, para iii, in the seventeenth week of pregnancy. The aneurysm ruptured five days prior to admission. She was successfully treated by a subtotal hysterectomy for exposure and ligation of the common iliac artery and vein. No previous report of an aneurysm of the external iliac artery during pregnancy could be found.

Ruptured renal aneurysm during pregnancy is quite rare, but two cases were found in a search of the literature. Ostling[10] reported three cases of ruptured aneurysms related to pregnancy; the renal, lienal, and hepatic arteries were, respectively, involved. The renal aneurysm ruptured shortly after full term. Ruptures in the elastica were found in all three cases.

Chisholm's[11] case was a rupture of a branch of the left renal artery in a 28-year-old patient seven months pregnant which occurred while walking. She was suddenly seized with severe back pain. When the abdomen was opened, the bleeding point could not be located and an extensive retroperitoneal hemorrhage was seen. Autopsy revealed a ruptured aneurysm of a branch of the left artery the size of a pea. She too was admitted the day following onset of pain and operated upon later that day because of persistence of symptoms.

The case now reported is that of a retroperitoneal hemorrhage during pregnancy. The patient's first baby was born at term in a hospital Dec. 17, 1939, one month after she sought prenatal care. She did not have an elevated blood pressure and her weight when delivered was 168 pounds. A normal spontaneous delivery followed a twelve-hour labor. Her second and third children were delivered at home by her mother-in-law.

The patient was a 33-year-old Mexican, gravida iv, para iii, whose last menstrual period was Jan. 29, 1951. At one o'clock in the morning of Aug. 25, 1951, she left her bed to go to the bathroom. As soon as she was on her feet severe pain located in the left upper quadrant and left lumbar region occurred. The severe pain continued, and fourteen hours following its onset, a doctor was called. Her blood pressure was 88/60, and she weighed 195 pounds. The pain was over the left lumbar region which was exquisitely tender to palpation. Because of the persistence of her pain and her pallor, she was hospitalized.

When she was seen in the hospital on the evening of Aug. 25, 1951, she was fairly comfortable. The blood pressure was 110/60; the pulse was 88 and regular. The pregnant uterus extended to one fingerbreadth above the umbilicus. The fetal heart tones could not be heard. The red blood count was 3,410,000, white blood count 15,600, polymorphonuclear leukocytes 81 per cent, lymphocytes 18 per cent, eosinophils 1 per cent, hemoglobin 70 per cent. A catheterized urine specimen showed 3 plus albumin, was negative for sugar, and there were eight to ten pus cells per high-power field; numerous bacteria and five to seven granular casts per high-power field were seen. Inasmuch as the blood pressure and general appearance had improved and because of the urinalysis and pain in the left renal area, a left pyelitis was suspected. During the night a 50 mg. Demerol tablet was given three times for pain, and 1,000 c.c. of fluid were taken by mouth.

At 6 A.M. she was catheterized and 300 c.c. of urine was obtained. On this morning severe pain in the left upper quadrant occurred upon awakening. At 8:30 A.M. the nurse found her pulseless, cold, and clammy. The blood pressure was 50/40; she was perspiring and

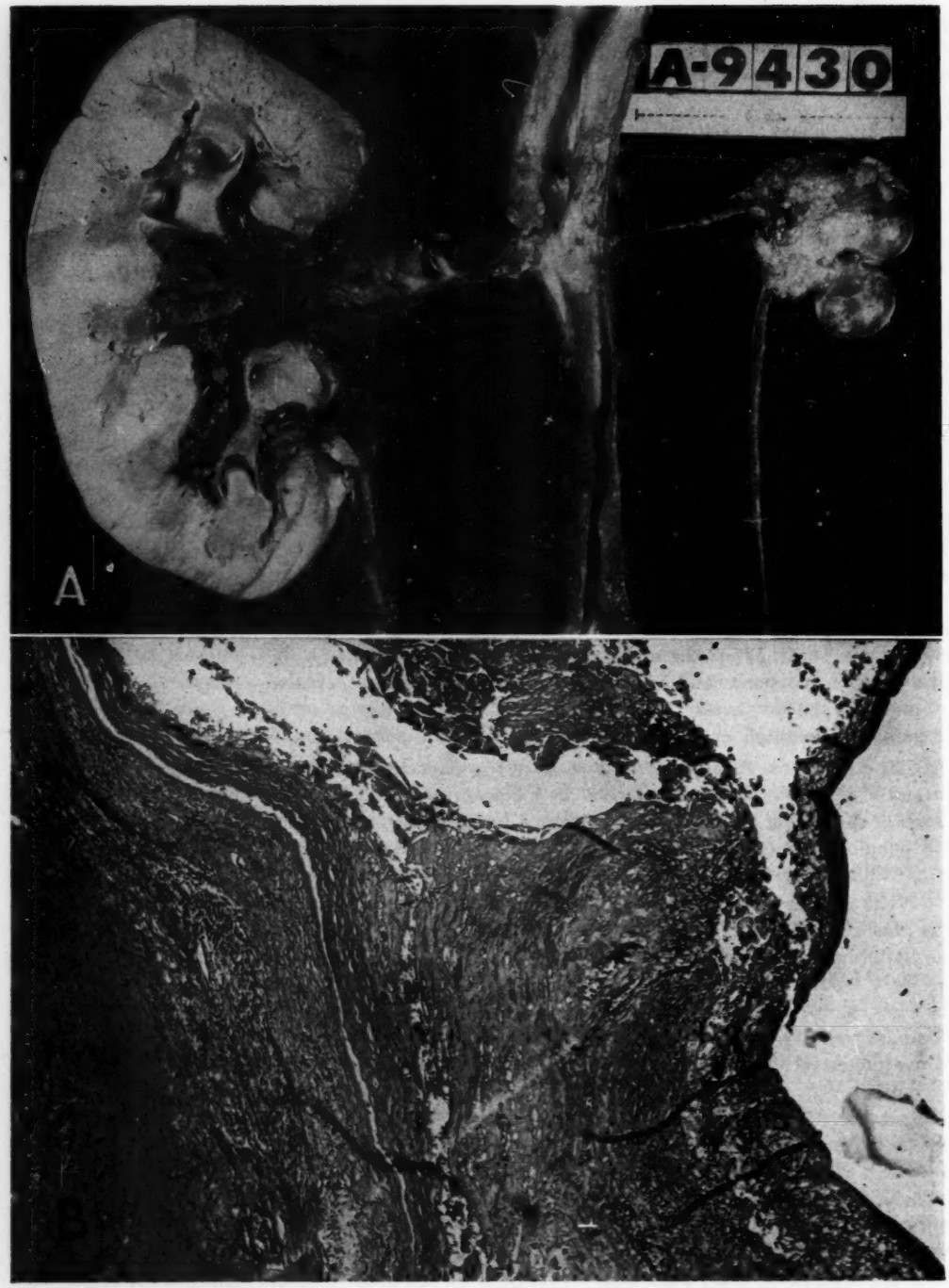

Fig. 1.

had sighing respirations. The red blood count had dropped from 3,410,000 to 2,300,000; the hemoglobin from 70 to 46 per cent. It was obvious that she was having a severe internal hemorrhage. Intravenous fluids and a blood transfusion were started. An abdominal paracentesis showed no blood. With fluid and blood running she was taken to the operating room.

Upon opening the abdomen a massive retroperitoneal hemorrhage was found which extended on the left side of the abdomen from the diaphragm to the anterior aspect of the left broad ligament. There was no free blood in the peritoneal cavity. When the gastrocolic ligament was detached from the transverse colon, the entire floor of the lesser peritoneal sac was found to be undermined with a tremendous collection of blood. The source of the bleeding could not be found, and the patient died as the abdomen was being closed.

Upon autopsy the findings shown in the photographs were as follows: Fig. 1, *A*, demonstrates the ruptured aneurysm of the left renal artery, the hyperplasia of the left kidney which weighed 360 grams, and the marked hypoplasia of the right kidney which weighed 10 grams. Microscopic examination of the right kidney revealed few tubules, very rare glomeruli, and no effective parenchyma. The aneurysmal wall showed much atherosclerosis, calcification, and hemorrhage. Atherosclerotic plaques were also present in the aorta. Fig. 1, *B*, is a section demonstrating the arterial changes which are pathogenic. The uterus was enlarged to a 6½ months' pregnancy and contained a male fetus corresponding to the period of gestation.

Summary.—Retroperitoneal hemorrhage is characterized by a delay between the onset of first hemorrhage and the final episode of bleeding. Ruptured aneurysm in pregnancy is more common in the splenic than the renal artery. The pathogenesis is usually congenital. Surgical intervention with adequate blood and fluids is the only chance of survival.

The Department of Pathology of the College of Medical Evangelists is thanked for their help and cooperation.

Addendum.—Since this paper was written, Zummo, Williams, and Uznanski[12] have reported 48 cases of retroperitoneal hemorrhage in pregnancy. Forty-four cases were found in the literature and 4 additional cases were presented. There were 7 patients who survived; 2 of the 33 who had splenic artery involvement are alive. All 7 of the patients with renal aneurysm died.

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1095 D Street

TUBAL MOLE ASSOCIATED WITH INTRAUTERINE PREGNANCY

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HYDATIDIFORM mole in the Fallopian tube is a relatively rare condition. Since no universally accepted criterion for diagnosis of a mole is available, the true incidence of tubal mole is not known. However, according to Chalmers,[1] only 15 cases have been recorded in the literature.

It is beyond the scope of this paper to attempt a complete review of the literature. The purpose of this report is to record another case of tubal hydatidiform mole, complicated by tubal rupture, which was associated with an apparently normal intrauterine gestation.

Case Report.—E. J., No. 47371, was a 26-year-old Negro woman who was first seen in the Maternity Clinic on Oct. 12, 1949. Her history revealed the following: she was gravida iii, para ii. The last menstrual period was June 10, 1949. The estimated date of confinement was March 17, 1950. She had had two previous uncomplicated pregnancies and deliveries. There was no history of previous hypertension. The physical examination was negative except for blood pressure of 150/100, and a uterus the size of a 4½ months' gestation, with an asymmetrical enlargement in the region of the right cornu, thought to be a uterine fibroid.

On Oct. 13, 1949, the patient entered the hospital complaining of sudden onset of lower abdominal pain, of 4 hours' duration, which persisted as a dull ache. Clinical examination revealed moderate tenderness in both lower quadrants, more on the right, with very little rigidity. The fundus uteri was palpable almost to the umbilicus. A tubular mass approximately 8 cm. in diameter extended at right angles from the region of the right cornu, was apparently continuous with the uterus, and of similar consistency. No fetal heart tones were heard. The blood pressure was 170/110 and the urine showed a trace of albumin. A diagnosis of intrauterine pregnancy, complicated by pre-eclampsia and a degenerating myoma, was made. X-ray examination revealed a fetal skeleton in the pelvis.

The patient improved and remained essentially asymptomatic until 2 A.M., Oct. 16, 1949, when she suddenly experienced a severe generalized abdominal pain, and was in shock when first seen. Examination revealed generalized abdominal tenderness and guarding and the blood pressure was 80/40.

Because of suspected intra-abdominal bleeding, a laparotomy was done as soon as possible. Exploration revealed the uterus enlarged to the size of a 4½ months' gestation. The right tube was dilated to approximately 8 cm. in diameter, with perforations on both the anterior and posterior surfaces, from which blood and "grapelike cysts" were exuding. Approximately 300 c.c. of blood was free in the abdominal cavity. Both ovaries were enlarged to approximately 6 to 8 cm. in diameter and contained multiple cysts.

A clinical diagnosis of tubal chorionepithelioma was made, and a supracervical hysterectomy and bilateral salpingo-oophorectomy were performed. A complete hysterectomy was not attempted because of the patient's poor condition.

Gross examination of the specimen revealed an apparently normal female fetus, 23.5 cm. in length, in the uterus. The infundibular portion of the right tube was filled with grapelike cystic masses typical of hydatidiform mole (Fig. 1).

The pathological diagnosis was: (1) tubal pregnancy with formation of a hydatidiform mole; (2) multiple lutein cysts of the ovaries; (3) intrauterine gestation, of approximately 4 months. No evidence of malignancy was found (Fig. 2).

The postoperative course was uncomplicated. Six weeks postoperatively, the blood pressure was 140/110, the urine was negative for albumin, an Aschheim-Zondek test was positive, and the pelvic examination negative. The patient failed to return as instructed and was next seen 8 months later on June 23, 1950. At this time, she was asymptomatic, the pelvic examination was negative, and the Aschheim-Zondek test was negative. The patient was followed at regular intervals through Feb. 12, 1951, and she remained asymptomatic. The pregnancy tests remained negative and pelvic examinations were not remarkable.

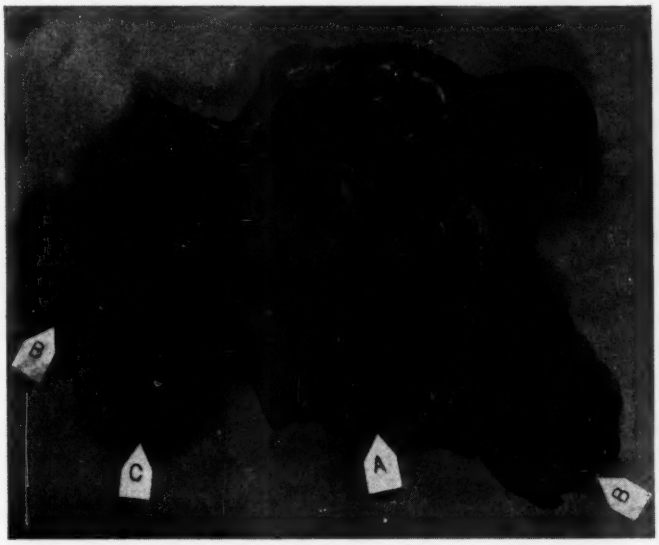

Fig. 1.—*A*, uterus; *B*, multiple lutein cysts; *C*, hydatidiform mole.

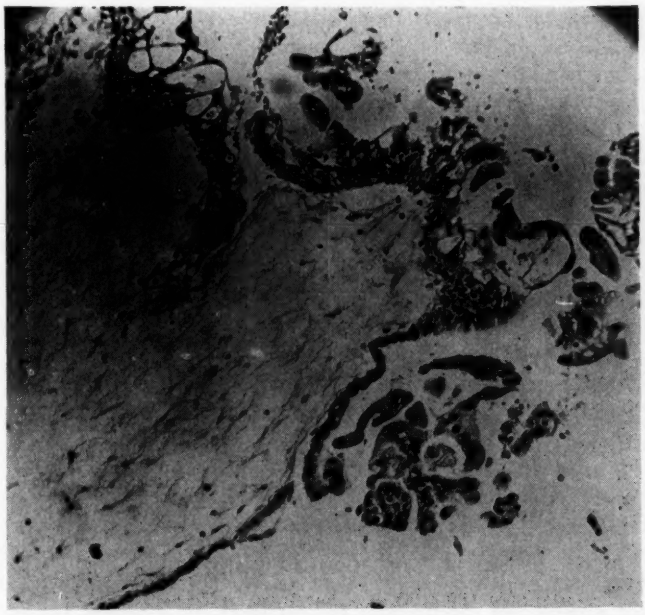

Fig. 2.—Microscopic section of tubal mole. Note the trophoblastic proliferation, myxomatous degeneration, and avascularity of the villus shown.

A case report of the relatively rare condition of a hydatidiform mole in the tube has been presented. The presence of the tubal molar gestation in association with a normal intrauterine gestation adds further to its interest as a medical oddity. The patient apparently recovered completely.

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ANENCEPHALOTHORACOPAGUS MONSTROSITY

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(From the Westlake Hospital)

A REVIEW of the literature reveals many reports of various types of monsters. Anger[1] reported a case of a double monocephalic female monster, one in which the head was developed and the two bodies were united at the abdomen, but separated below the umbilicus. Plummer and Scheffer,[2] Phalen and Abbott,[3] Mackay,[4] and Abbott and Kaufmann[5] have also reported similar cases. However, there has never been a case report of an anencephalothoracopagus monster—two monsters with one undeveloped head, and two complete bodies united at the thorax but separated below the xiphoid process (Fig. 1). X-ray revealed bony fusion at the level of the base of the skull (Fig. 2).

M. S., a Negro woman, aged 26 years, para v, gravida vi, whose expected date of confinement was Feb. 28, 1952, was first seen when she was four months pregnant. Her previous deliveries were all vaginal and uncomplicated, with three living male and two living female infants. There were no anomalies in any of the children.

The physical examination revealed a well-developed, well-nourished Negro woman, whose general physical condition was ascertained to be good and who had no presenting complaints. The uterus was enlarged to 12 cm., the adnexa were clear, and the cervix was normal. Pelvic measurements were within normal limits. The red blood count was 4.4 million, hemoglobin was 12.2 Gm., and the white blood count was 6,400, with a normal differential count. The blood type was A and the Rh factor positive. The Kahn test was negative, and the urine free of albumin and sugar. The prenatal course was uneventful for the first two trimesters. Urine and blood pressure were normal for the first seven months of pregnancy. When seen in the eighth month of pregnancy, the abdomen seemed unusually large for this period, and a clinical diagnosis of polyhydramnion was made. At that time, Jan. 24, 1952, a single flat plate x-ray of the abdomen was taken and failed to reveal the presence of a normal fetal head. A diagnosis of anencephalus was then made and the patient was requested to return for another x-ray, which she did not do. She was not seen again until 11 A.M., Jan. 27, 1952, when she entered the hospital in active labor. At this time the fetal heart tones, which were 140 on previous occasions, were not heard. The fetus was assumed to be dead.

X-rays of the abdomen for fetal parts were ordered, but labor progressed too rapidly, and the patient spontaneously delivered a 6½ pound stillborn female monster. The time of death was estimated at eight to ten hours prior to delivery. Polyhydramnion was confirmed at the time of delivery, and the total labor was four hours. Analgesia consisted of scopolamine hydrobromide, 1/200 grain, and Demerol, 100 mg., which were given three hours prior to delivery when the cervix was 3 to 4 cm. dilated. After Credé delivery of the placenta, which was normal, a pelvic examination revealed a fibroid uterus measuring 12 cm. The postpartum course was uneventful and the patient was discharged six days after delivery.

The monster measured 38 cm. (crown-heel) and weighed 6½ pounds. There were a single placenta and a single umbilical cord entering one umbilicus. The two bodies were united at the thorax (thoracopagus), and the head was single and not fully developed (anencephalus). The two sets of limbs were perfectly formed and equal in size. Further pathological examination was not performed in order to preserve the specimen.

The theories of the etiology of monstrosities are varied, but among the more common are placental infarcts, as reviewed by Talbot,[6] and fetal anoxia during cranial development, as described by Olim and Turner.[7] However, neither of these factors was noted in this case.

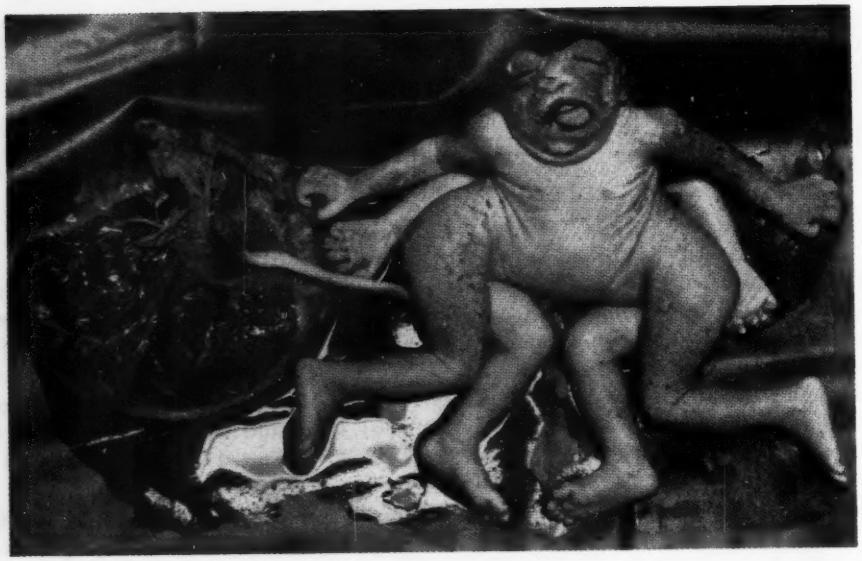

Fig. 1.

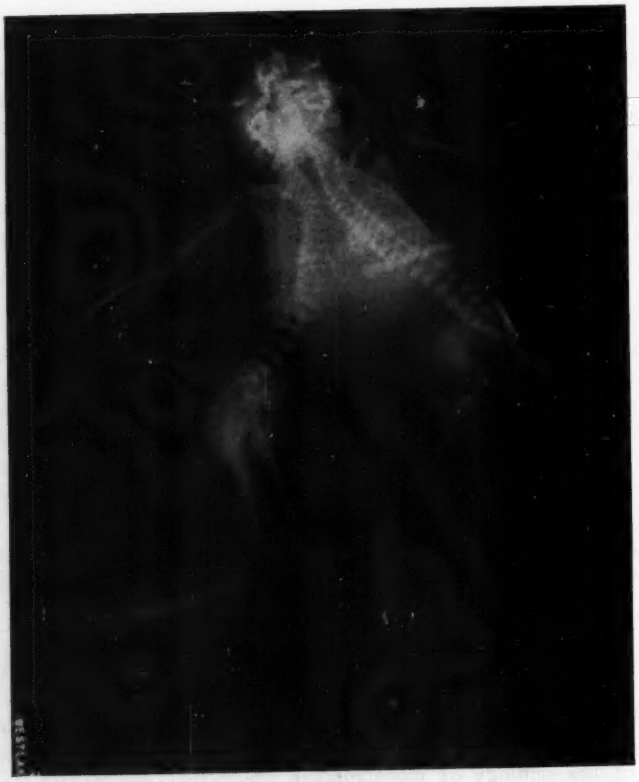

Fig. 2.

Summary

A case of anencephalothoracopagus monster is reported for the first time and described. References are made to similar, but not identical, monsters. No etiological factor was elicited in this case.

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DOUBLE SURVIVAL OF MONOAMNIOTIC TWINS

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THIS is a case report of monoamniotic twins with survival of the infants. It is of interest because there have been relatively few such reports in the literature. Quigley[9] quotes Rosenberg as stating that monoamniotic twins occur once in 60,000 pregnancies.

In 1935 Quigley[9] reported 108 cases of monoamniotic twins which he had collected from the literature and added one case of his own. Out of this number 20 cases resulted in a single live birth, and another 17 resulted in double live births. He calculated the chance of double live births to be 15 per cent.

Eight of Quigley's cases were reported to be from the American literature. Jones[5] states that one which he included (a case reported by Boyd in 1883) was of a single fetus papyraceus in a single amnion. Of his 8, only one case resulted in a single live twin.

In his review, Quigley[9] presents a case of Podzahrodsky which is very similar to the one presented by us. He reports a case in which a midwife cut a cord which was tightly wound about the neck of the first twin. "It proved to be the cord of the second twin and only by prompt delivery effected by Podzahrodsky were both twins saved."

Coulton, Hertig, and Long[3] in reviewing the literature in 1947 found 5 cases in the English literature since Quigley's report and added 2 of their own. These 7 cases are reviewed briefly.

In 1935 Rucker[10] reported a case of monoamniotic twins in which the first twin had both cords around his neck. The second twin in this case was macerated. There was a true knot uniting the cords which is not an uncommon finding in these cases.

In 1935 Litt and Strauss[6] reported a case of monoamniotic twins in which one was normal and the other anencephalic. There were multiple true knots in the cords. Both infants were stillborn, having been delivered approximately five weeks prematurely.

In 1936 Frewer[4] reported a case in which the first child survived, and the second died 30 hours later.

The first case of double survival in the American literature was that reported by Parks and Epstein[8] in 1940. The twins were approximately one month premature. The cords were united in a true knot.

In 1942 Jones[5] reported a case of monoamniotic twins delivered at seven and one-half months. One was a macerated premature infant and the other a flat papyraceus. Their cords were joined in a true knot, and there was also a true knot in each of the cords.

In 1946 Acosta-Sison, Aragon, and de la Paz[1] reported two cases of monoamniotic twins. The first case was one in which the cords were knotted. The first child was born alive; but the second one, born thirty minutes later, was stillborn. The other case they reported was one of double survival of monoamniotic twins delivered by Cesarean section because of eclampsia.

In May, 1947, Boyle and Richter[2] reported a case of true knots in the umbilical cords causing the death of both twins in utero in the seventh month.

In July, 1947, Coulton, Hertig, and Long[3] added two cases of double survival. Their cases were unique in that there was neither knotting nor tangling of the cords.

Mendel[7] in 1951 reported a case of monoamniotic twins in which the first baby was viable, and the second was macerated.

In 1947 Coulton's[3] review of the literature brought Quigley's report up to that date. With the addition of the cases of Acosta-Sison, Boyle, and Mendel (which have appeared in the literature since that review), there have been 11 cases of monoamniotic twins reported in the English literature since Quigley's review in 1935. The addition of the following case will bring the total to 12. Six of these cases have resulted in double live births. One of these resulted in a neonatal death so that there remain only 5 cases of double survival.

Case Report

CASE A83542.—This 19-year-old white married woman, para i, gravida ii, was followed during the antepartum period by one of us in a Public Health Clinic. The last menstrual period was Aug. 7, 1951. She had no complications other than slight edema of the ankles. On May 14, 1952, a twin pregnancy was diagnosed on abdominal examination, and this was confirmed by x-ray.

Labor began at 7:30 A.M. on July 24, 1952. The membranes ruptured at 7:35 A.M. On admission the head was crowning. The patient was taken directly to the delivery room and anesthetized with nitrous oxide, oxygen, and ether. The first fetus presented in left occipitoanterior position and was delivered by low forceps with an episiotomy. The cord was found to be looped twice around the neck of the first baby. It could not be slipped over the head or shoulders and was clamped and cut. Upon completion of the delivery it was found (to the surprise of the operator) that the cord which had been cut supplied the second twin, still in utero.

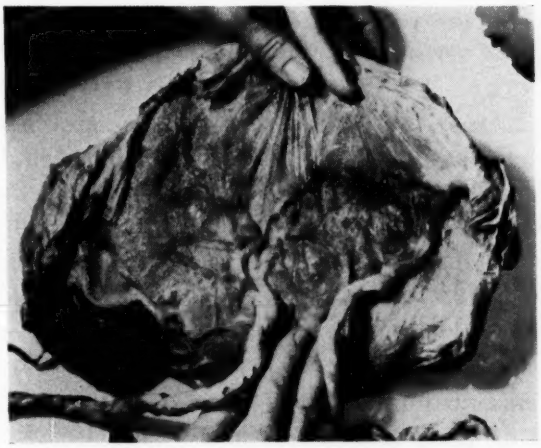

Fig. 1.

This cord was also knotted with the cord which supplied the first fetus, so that the latter could not be removed without untying the knot. The umbilical cords measured 71.5 cm. and 86.5 cm., respectively.

A version and extraction from left occipitoposterior position were then done on the second twin, and a live baby resulted. Four minutes elapsed between the completion of the first and second deliveries. The latter was finished at 8:20 A.M.

The babies were male infants weighing 5 pounds, 15 ounces, and 5 pounds, 4 ounces, respectively. They breathed and cried spontaneously. The second twin did not suckle as strongly during the second day as the first, but this was not noticed the third day. They were discharged on July 27, 1952, in good condition weighing 5 pounds, 9 ounces, and 4 pounds, 15 ounces. They are still living at this writing, Oct. 27, 1952.

The placenta weighed 1,040 grams and was roughly circular and 21 cm. in diameter. There were two umbilical cords, and the attachment of each was 3.5 cm. from the edge of the placenta. Their insertions were 7 cm. apart. Careful inspection of the fetal side of

the placenta revealed no segments of amniotic membrane between the attachments of the umbilical cords and in no place at the periphery was there any evidence of two amniotic layers. The maternal side was not remarkable.

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Editorial

The Prophylaxis of Gonorrheal Ophthalmia Neonatorum

DR. GEORGE KOSMAK, the Advisory Editor, forwarded a letter from Dr. M. Leff, who suggested that the JOURNAL join in a campaign to abolish the law in 32 states which requires the instillation of one drop of a 1 per cent solution of silver nitrate into each conjunctival sac of the newborn infant and, in the remainder of the states, the requirement that this solution or some allied solution be used. Although the editor has been in a full-time position since 1921, he has seen very few cases of gonorrheal ophthalmia. In the period from 1931 to March 1, 1953, there have apparently been no cases (Record Room) of gonorrheal ophthalmia at the Chicago Lying-in Hospital where all patients have been kept until the tenth postpartum day or longer with but few exceptions and those during the past few years.

Since there have been some reports published advocating that silver nitrate solution no longer be used prophylactically in the newborn infant's eyes, it was decided to send questionnaires to those hospitals which had 4,000 or more deliveries. One hundred questionnaires were mailed, usually to the chief of obstetrics, and the pediatrician in charge of the newborn nurseries and to various ophthalmologists. Of the 35 hospitals to which questionnaires were sent, replies were received in all instances; sometimes from obstetrician, pediatrician, and ophthalmologist.

An excellent editorial on this subject was published in the *Journal of the American Medical Association,* which stated that prior to the introduction of silver nitrate prophylaxis in 1882, the incidence of ophthalmia neonatorum in the Leipzig Lying-in Hospital was 10.8 per cent and it was reported to be over 10 per cent in other obstetric clinics throughout the world. Similarly, the incidence of blindness from ophthalmia neonatorum in 22 German asylums was 30 per cent in 1867. After the introduction of the Credé method, the incidence of ophthalmia neonatorum in the Leipzig institution and other obstetric clinics fell to less than 1 per cent, and the incidence of blindness from ophthalmia neonatorum in the asylums for the blind fell proportionately. The editorial concluded, "While there is much truth in both sides of the controversy, the weight of the argument appears to oppose the abandonment of silver nitrate. Thus, while there can be no possible objection to the use of penicillin prophylaxis in hospital clinics where its use is well controlled, it would appear that any specific recommendation for changes in the state laws or regulations would at this time be premature. It is, however, quite possible that further investiga-

tion will permit firm recommendations for a prophylactic or prophylaxis with an antibiotic with a wider spectrum than is possessed by penicillin, and without the objections that can now be made against the penicillin procedure."

Davidson wrote an excellent review of this subject in 1952, pointing out that penicillin as drops, ointment, or intramuscularly caused conjunctivitis in, at the most, 15 per cent of the eyes, but silver nitrate solution caused varying degrees of irritation in 50 per cent or more. Neither substance would completely prevent gonococcal conjunctivitis.

The Editor had experience with one near catastrophe in which 15 babies had 10 per cent silver nitrate solution (mistake by pharmacy) instilled into each eye. Fortunately, for some years we had been flushing the eyes after the silver nitrate instillation with 0.9 per cent sodium chloride solution. Despite the partial neutralization of the $AgNO_3$ solution, all of the babies had a severe chemical conjunctivitis and it was only through the untiring efforts of the ophthalmologist that only two babies had some scarring of the cornea and in both instances it was not near the pupil. The babies were followed by ophthalmologists even if the parents took them to other states. A change to the wax ampules reduced the possibility of concentration through evaporation of the silver nitrate solution and certainly reduced the likelihood of an incorrect concentration.

Fifty-two per cent of the doctors answering the questionnaires favored the discontinuation of 1 per cent silver nitrate to the newborn infant's eyes. Thirty-five per cent thought it should be continued and 13 per cent had no definite view. Of the 17 doctors who wished to discontinue silver nitrate solution, 12 thought that penicillin should be substituted. One gave penicillin intramuscularly to the mother 12 hours before delivery; 3 wanted to use nothing; and 1 desired an irrigation with a water solution.

Experiences with the prophylactic use of agents other than silver nitrate solution are rare. Eastman at Johns Hopkins Hospital reported a series of more than 22,000 cases in which penicillin was used with no proved case of gonorrheal ophthalmia. Leff reported 4,500 cases in which only water was used.

Cosgrove stated that at the Margaret Hague Maternity Hospital they have had approximately 150,000 deliveries in the period 1930 to 1952 with 38 cases of gonorrheal ophthalmia and that nongonorrheal conjunctivitis is rare. Storrs and Unsworth reported that during the past five years, with 28,000 deliveries, using $AgNO_3$ solution, they have had only one case of gonorrheal ophthalmia.

In the period 1931 to March 1, 1953, over 70,000 babies have been born in the hospital and 6,700 in the former home delivery service. All were treated with 1 per cent $AgNO_3$ solution and our records show no case of gonorrheal ophthalmia.

Shaw stated that there were 242,662 births in California in 1950, with only 10 cases of gonorrheal ophthalmia, an incidence of 0.004 per cent. He asks, "Is there any reason to continue by statute and custom an anachronistic preventive method which in itself is not without harmful effects?"

Allen, St. Louis Maternity Hospital, states that they have studies planned but that gonorrheal ophthalmia is rare. He also stated that routine cultures for the gonococcus have been discontinued in new obstetrical and gynecological patients because it cost over $800.00 for every positive culture.

Series comprising hundreds of thousands of babies treated prophylactically with $AgNO_3$ solution are available with no gonorrheal ophthalmia neonatorum. The absence may be due to the $AgNO_3$ solution or to the fact that the mother had no gonorrheal vaginitis at delivery. Certainly, many private or service patients from the hospital's own outpatient clinics delivered in the hospital will have no gonorrheal vaginitis at delivery because it was detected in sufficient time for prompt treatment. Thus, the prophylactic treatment in such hospitals with $AgNO_3$, or silver proteinate solutions, penicillin drops or injections, flushing of the eyes with water or 0.9 per cent saline solution, etc., is of no value for determining the prevention of gonorrheal ophthalmia.

TABLE I

YEARS	NO. BABIES TREATED	TREATMENT	CONJUNCTIVITIS			
			NONGONORRHEAL		GONORRHEAL	
			NO.	%	NO.	%
John Gaston Hospital.—						
1945 and 1946	4,587	$AgNO_3$	39	0.85	11	0.24
1950 and 1951	8,408	Penicillin drops	6	0.07	7	0.08
1948 to 1952	20,485	Penicillin drops	29	0.14	8	0.04
Gallinger Municipal Hospital.—						
1948 to 1950	3,159	$AgNO_3$	135	4.5	6	0.19
1948 to 1950	2,586	Penicillin—50,000 units intramuscularly	39	1.8	7	0.27
1950 to 1952	3,255	Penicillin—150,000 units intramuscularly	35	1.2	3	0.09
1950 to 1952	4,880	$AgNO_3$	193	4.2	10	0.20

Data in Table I show that penicillin drops for one dose decreased the incidence of gonorrheal ophthalmia and of nongonorrheal conjunctivitis at the John Gaston Maternity Hospital in Memphis, Tenn. A comparable series treated with $AgNO_3$ solution at the Gallinger Municipal Hospital in Washington, D. C., showed an incidence of gonorrheal ophthalmia neonatorum of 0.20 per cent, about the same as at the Gaston Maternity, 0.24 per cent. An intramuscular prophylactic injection of 50,000 units of penicillin at the Gallinger Hospital did not prevent gonorrheal ophthalmia but 150,000 units caused an appreciable decrease in the incidence of gonorrheal ophthalmia. This latter hospital had an incidence of 1.5 per cent of nongonorrheal conjunctivitis in babies who received penicillin and of 4.4 per cent in babies treated with $AgNO_3$ solution. In contrast, the Gaston Hospital reported an incidence of 0.85 per cent of nongonorrheal conjunctivitis in babies treated with $AgNO_3$ solution and of 0.14 per cent in penicillin-treated babies. These two sets of data are difficult to interpret.

The incidence of nongonorrheal conjunctivitis has markedly decreased in our hospital since we began to flush the eyes with 0.9 saline solution. After the

1 per cent $AgNO_3$ solution has been properly dropped into each eye (this procedure requires two people to perform it adequately) approximately 30 per cent of the babies have a slight to moderate discharge, but all cases clear up promptly without treatment.

The personal reports from pediatricians and especially from ophthalmologists about whether or not gonorrheal ophthalmia neonatorum can be easily cured without damage to the eyes are also conflicting. Some doctors state that it can be easily cured with no damage and others report scarring of the cornea or even perforation.

Sanford states that despite $AgNO_3$ solution, gonorrheal ophthalmia occasionally occurs in babies at Cook County Hospital; they are not easily cured and permanent damage occasionally results.

Chiefs of large obstetrical services, the pediatricians in charge of the nurseries, and ophthalmologists as individuals and their society actions show no agreement on the prophylactic value of $AgNO_3$ solution, penicillin drops or parenteral injections, water or saline irrigations, or no treatment to the baby's eyes at birth.

Since most maternity services have such a low incidence of gonorrheal ophthalmia, because of either the detection and treatment of gonorrheal vaginitis during pregnancy, or the prophylactic use of silver nitrate solution, their results are not comparable to those of an institution where patients enter who have had no prenatal care or in whom possibly the prophylactic administration of the silver nitrate solution was not properly carried out. It is worth noting that, at the Gallinger Hospital, in the 4 series of babies treated, gonorrheal ophthalmia was present in each series and it was only in the group of babies who received the large amount of penicillin that the incidence was decreased but even in that group the number of cases of gonorrheal ophthalmia was much greater than is encountered in most maternity services.

The Editor, having read many reports of the prophylactic use of silver nitrate solution in newborn infants as well as the personal communications which many doctors were kind enough to send him, concludes that the available evidence on the *prevention* of gonorrheal ophthalmia by the instillation of 1 per cent silver nitrate solution, or of penicillin solution, or the injection of penicillin intramuscularly into the baby is not conclusive. There is certainly insufficient evidence to justify legislation permitting the use of some other prophylactic agent.

The editor believes that 10 or more of the maternity services which have parturient patients with gonorrheal vaginitis and which deliver 5,000 or more babies per year could within one year obtain sufficient evidence to determine whether or not: (1) the prophylactic use of silver nitrate solution warranted its use; (2) penicillin drops were better than $AgNO_3$ solution; and (3) the injection of aqueous procaine penicillin warranted its use. Until an adequate number of babies with proper controls in hospitals where patients still have gonorrheal vaginitis at delivery are treated with $AgNO^3$ solution or some

form of penicillin, no attempt should be made to influence state health departments to change the laws regarding the prophylactic use of a silver nitrate solution at birth.

Wm. J. Dieckmann.

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Department of Reviews and Abstracts

CONDUCTED BY GEORGE W. KOSMAK, M.D., NEW YORK

Selected Abstracts

Puerperium

McNally, Hugh B., and Ehrlich, Daniel: Postpartum Hematomata, South. M. J. 45: 708, 1952.

The authors present a résumé of 52 cases of postpartum birth canal hematomas. The predisposing causes are primiparity, prolonged second stage of labor, failure to perform episiotomy early enough, and faulty episiotomy repair. Factors which sometime have been suggested as predisposing causes, but in this study were not found to be so, are: age of patient, type of delivery, anesthesia, size of baby, toxemia, variocosities, and blood dyscrasias.

Failure to make an early and prompt diagnosis is too often a major calamity in puerperal hematomas of the birth canal. Most of them can be prevented by careful inspection and palpation of the soft tissue of the vagina following the performance of episioperineorraphy. The treatment of postpartum hematomas begins with early recognition. Prompt evacuation of the clots and accumulated blood is followed by ligation of the bleeding vessel if it can be found, which it usually cannot. The cavity should be packed loosely with hemostatic absorbable sponges and the vagina packed tightly with ordinary gauze packing. Transfusion should be carried out if necessary and prophylactic antibiotics administered to prevent infection.

WILLIAM BICKERS

Radiation

Martins, A. Francia: Aspects of Radiotherapy in the Treatment of Cancer of the Cervix, Rev. paulista de med. 40: 52, 1952.

The author has made a rapid survey and study of the reaction of living tissues under the action of all modalities of radiotherapy as well as radio-sensitivity of these living tissues. In reviewing the basic laws of radiobiology, he explains the mechanism of cellular death by actinic rays, as well as the healing phenomena of cancerous tissues by scar formation. Through his experiences the author proves the old dogma of tissue differentiation as related to the eventual outcome of the treated case. He finds that the more the tissues are differentiated, the less malignant and more radioresistant they are, and by the same token the less differentiated are more malignant and more radiosensitive. However, being aware of the clinical varieties of these classic concepts, the author makes a plea for thorough study and evaluation of every case individually, so as to decide on the best method of treatment, since the knowledge obtained through direct study of patients is a factor of great importance in obtaining better results.

Following the above general considerations, the author presents fourteen cases of cancer of the cervix treated with all types of radiotherapy modalities, and including all the complications encountered, such as fistulas, strictures, telangiectatic reactions of tissues, etc. The fact is also brought out that the Wertheim procedure is still used in cases where this operation is indicated.

RICARDO L. GORBEA

Sterility, Fertility, Contraceptives

Sandler, Bernard: The Relation of Cervical Mucus and Asthenosperma to Sterility, J. Obst. Gynaec. Brit. Emp. **59**: 202, 1952.

In the study of sterility, examination of both the husband and the wife is necessary, including the Sims postcoital test on the wife. Even though the semen of the husband may be found to be below standard for fertility (subfertile), if there is an abnormal condition of the wife's cervix with excess secretion "hostile" to the spermatozoa, adequate treatment of the cervicitis may result in pregnancy, even though the husband's semen remains subfertile. Illustrative cases are reported. In a study of 205 cases of sterility, the cervix was found to be clinically abnormal in 108 cases; in 16 of these cases, infection of the cervix with *B. coli*, streptococci, or coagulose-positive staphylococci was demonstrated; in one case a pleuropnenumonia-like organism was found. While women coming to a gynecological clinic for treatment have definite symptoms of cervicitis, women examined in a sterility clinic complain of no such symptoms and may even deny any excessive vaginal discharge, although examination shows the cervix bathed in pus. Adequate treatment of this condition is necessary before conception can take place.

HARVEY B. MATTHEWS

Toxemia

Mcintosh, R. R.: The Significance of Fits in Eclampsia, J. Obst. & Gynaec. Brit. Emp. **59**: 197, 1952.

The convulsions of eclampsia resemble those of so-called ether or anesthetic convulsions, and those of idiopathic epilepsy and electroshock therapy. Studies of the electroencephalogram in idiopathic epilepsy have shown an abnormal rhythm designated as cerebral dysrhythmia. Similar electroencephalographic abnormalities have been demonstrated in about 12 per cent of apparently normal persons who have shown no symptoms of epilepsy. It is probable that these persons are more prone to develop convulsions. Studies by other investigators of persons who had developed convulsions under anesthesia and of patients who had had eclamptic convulsions, have shown that a high percentage (65 to 73 per cent) show cerebral dysrhythmia in their normal state. The author has made an electroencephalographic study of 6 patients who had had eclamptic convulsions at varying periods after their delivery and discharge from the hospital; 5 of these 6 patients showed cerebral dysrhythmia. These findings indicate that eclamptic fits are not a real indication of the severity of the toxemia of pregnancy, as persons who are prone to convulsions as indicated by cerebral dysrhythmia may develop fits with a less serious degree of toxemia than those whose cortical discharges are more stable. In some women toxemia may be so severe as to cause death by cerebral hemorrhage, cardiac failure, cortical necrosis of the kidneys, and liver necrosis, without eclamptic fits developing at any time. Two illustrative cases are reported.

HARVEY B. MATTHEWS

Tubal Insufflation

MacGregor, W. G., and Oliver, R.: Hysterosalpingography: To Screen or Not to Screen, Lancet, **2**: 563, 1952.

In an uncomplicated case, tubal patency can be demonstrated with 15 to 18 seconds of fluoroscopic screening and a single film. If the tubes do not fill, or do not empty into the peritoneal cavity, more films and a longer screening period are necessary, since apparent blockage is often transient and functional.

The radiation dose to the ovaries during a screening period of several minutes, and with several films, is not inconsiderable. Conceivably, ovarian damage with genetic mutation effects could follow. To measure this dose, the authors have used ionization chambers in

four patients and in a cadaver. While the measured exposures are less than previously estimated by others, the authors do recommend several measures to shorten screening time. They also suggest protection of the operators by shielding devices and methods of reducing scatter.

IRVING L. FRANK

Mübius, M.: Hysterosalpingography, Zentralbl. f. Gynäk. **74**: 1295, 1952.

Hysterosalpingography, which has been employed for over 30 years as a diagnostic measure in female sterility and other gynecological disorders, is a procedure which is not without its inherent dangers. In the beginning the use of barium and other opaque media caused many untoward results, but with the advent of iodized oils and iodine aqueous solutions, many of the basic dangers were eliminated. Because of this, hysterosalpingography has become a routine procedure for studying intrauterine pathology as well as tubal pathology and patency. However, it is brought out, there are so many inherent dangers in the procedure, that, in the case of sterility, all other tests, including sperm study, ovulation studies, and gas determinations of patency should be completed before iodized solutions are injected. The fundamental dangers are the spread of chronic or acute infection of the pelvis and oil embolism. Therefore, the author feels that previous or present inflammation, not only of the tubes but of the cervix as well, may be rekindled by the procedure, and that this, therefore, is a contraindication to the test.

Once infection is ruled out, the other dangers can be minimized by a routine which is described in detail. Special precautions include a previous antiseptic vaginal douche, the use of a good cannula and occluding olive, gentle cervical dilatation, and controlled pressure. The optimal time for hysterosalpingography is during the early secretory phase of the menstrual cycle, since during the follicular phase tubal spasm may be present and during the late luteal phase the endometrium is so thick that it closes the ostium of the tube. This optimal time is considered to be the sixteenth to the eighteenth day of a normal 28 day cycle. The test itself always should be conducted under fluoroscopic control with injection of the opaque medium being done very slowly and continually observed. The amount of oil which is used should not be more than 2.0 c.c. except where the uterus is enlarged or when myomas are suspected, then a maximum of 4.0 c.c. may be introduced into the cavity of the uterus. These quantities are actually the amounts which are injected and do not include the material necessary to fill the cannula or connecting tubes. The author decries the use of larger volumes since postmortem studies of uterine cavities showed that a normal uterus and tubes can retain only a maximum of 3.0 c.c.

The amount of x-ray used is without danger. Only two plates are necessary, one after the cavity is filled and one 24 hours later to observe peritoneal spill. To obviate psychic or other spasm, 20.0 mg. of Proluton and 0.25 to 0.5 mg. of atropine sulfate are administered intramuscularly, one-half to one hour before the test is started. More recently 0.5 mg. of nitroglycerine was administered orally. When nitroglycerine was used the number of tubal occlusions decreased from 25 to 9 per cent.

Besides the value of hysterosalpingography in demonstrating carcinoma or submucous myomas of the fundus, tuberculosis of the female genital tract, and other pathological conditions, it also has a great therapeutic effect in sterility. By employment of this procedure in a large series of sterility problems where no definite cause could be determined, 25 per cent of all patients studied became pregnant within 6 months. Mild complications developed as the result of the procedure in 0.6 per cent. No major complications were encountered and no deaths occurred. The author feels that in general usage, when unsuitable cases are eliminated, hysterosalpingography is better than tubal insufflation because it demonstrates the exact point of closure of the tubes in the light of surgical intervention, and also because the iodized oil has a definite salpingolytic effect which often results in developing patency of previously closed tubes.

L. B. WINKELSTEIN

Vaginal Infections, Trichomonas

Bauer, Helmuth: Pathogenicity of Trichomonas Vaginalis in Women, Zentralbl. f. Gynäk. **74:** 246, 1952.

The pathogenicity of *Trichomonas vaginalis* in women has never been clearly understood. It has been felt that although acquired by the male by coitus, it was not returned to the female in a like manner. The question has been further complicated by the fact that three definite similar organisms have been isolated: *T. vaginalis,* found in the urogenital tract; *T. buccalis,* found in the mouth; and *T. intestinalis,* which is present in the gastrointestinal canal. Although all three appear similar microscopically, the question has never been fully resolved as to whether they are the same or different protozoans, or whether they can all adapt themselves to the same environmental conditions. Because of a tremendous epidemic in cows in Weisbaden in 1934 to 1936, all organisms were thought to be the same because they all were isolated from the blood, milk, secretions, and excretions. The author has attempted to settle both the question as to whether the spread of *T. vaginalis* is by coitus, and also whether the various forms of the organisms are the same, by means of transplantation of infected secretions into healthy urethras and vaginas. In no instance was he able to produce any symptomatology in the male by transference of positive vaginal secretions into the urethra. Furthermore, in a group of over 45 women previously proved to be free of any trichomonad infection by both repeated smear and culture techniques, he was unable to produce either objective or subjective evidence with the inoculation into the vagina of contamined secretions of either *T. tenax* or *T. intestinalis.* Conclusions are therefore reached that (1) these are separate and distinct protozoan organisms each having its own habitat, and (2) they are probably not spread to the male or to the female by infected coitus.

L. B. WINKELSTEIN

Correspondence

A Note on the Use of Rana Pipiens Schreber in Pregnancy Diagnosis

To the Editor:

The use of the American frog *Rana pipiens* in pregnancy tests has received considerable attention from clinicians and experimentalists during the past several years. One of the most difficult-to-assess problems presented by available data is the wide variation in proportion of false negative values obtained. Such false negatives vary from as many as 44 per cent[1] to none.[2] These data are not directly comparable, as Gardner and Harris considered all specimens studied in their calculations, whereas the Wiltberger and Miller value is for the first trimester only. Gardner and Harris, however, had a much higher proportion of false negatives during the first trimester (>10 per cent). Presumably much of this variability is the result of differential sensitivity of the frogs utilized. This discrepancy has recently been noted by Robbins,[3] who reports that insensitivity has been no problem in his studies.

The purpose of the present communication is to suggest a possible explanation of this phenomenon, which hardly seems explicable entirely on the basis of seasonal variability. It is a fact that the American frog known as *Rana pipiens* represents a complex of populations which differ radically in physiological, but not in morphological, characteristics. Moore[4] has recently shown that northern populations of this species differ from southern in embryonic temperature tolerance, rate of development, temperature coefficient, egg size, and form of egg mass. In another paper[5] he has shown that crosses between specimens from northern and southern populations result in numerous morphological abnormalities, and a marked retardation in developmental rate. He states that in these cases intraspecific hybridization is less successful than certain interspecific crosses. Thus specimens from certain portions of the range of *Rana pipiens* differ physiologically from specimens from other portions of the range as much as if not more than they do from related species. In the light of this information the discrepancies noted above are to be expected, if the frogs used were obtained from different portions of the geographic range of *Rana pipiens*. Unfortunately the papers noting these wide differences do not record the geographical origin of their material. If one assumes that the frogs used by Gardner and Harris were collected near the area in which they worked (Texas), those used by Wiltberger and Miller were collected where they worked (Ohio), and those by Robbins where he worked (Boston), the discrepancies are certainly understandable. Before this frog pregnancy test can be adequately evaluated, the relative sensitivity of frogs from varying geographic regions must be assayed.

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MARCH 25, 1953.

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Items

American Board of Obstetrics and Gynecology

The Directors of the American Board of Obstetrics and Gynecology wish to express their thanks to the following gentlemen who responded so willingly to our request for help in proctoring the recent written examinations on Feb. 6, 1953:

Drs. T. W. Adams, Portland, Ore.; William C. Ahlering, Cincinnati, Ohio; Walter J. Balzer, Davenport, Iowa; William J. Blackwell, Evanston, Ill.; Eric H. Blank, New London, Conn.; George P. Bohlender, Erie, Pa.; Thomas M. Boulware, Birmingham, Ala.; Herbert E. Bowles, Honolulu, Hawaii; Edmund A. Brannen, Macon, Ga.; Philip N. Bray, Duluth, Minn.; Willis E. Brown, Little Rock, Ark.; Preston T. Brown, Phoenix, Ariz.; Albert J. Carsen, San Jose, Calif.; Henry W. Clapp, Muskegon, Mich.; Irving Chrisman, Paterson, N. J.; C. J. Collins, Orlando, Fla.; H. F. Connally, Jr., Waco, Texas; S. A. Cosgrove, Jersey City, N. J.; George E. Cowles, Wichita, Kan.; Charles B. Darner, Fargo, N. D.; Russell R. de Alvarez, Seattle, Wash.; A. W. Diddle, Knoxville, Tenn.; Joseph W. Douglas, Pensacola, Fla.; Nicholson J. Eastman, Baltimore, Md.; William C. Eller, Waterloo, Iowa; O. A. Ellingson, Tampa, Fla.; James B. Eskridge, Jr., Oklahoma City, Okla.; David Findley, Omaha, Neb.; J. P. Gardiner, Toledo, Ohio; Rafael A. Rivera Gil, Santurce, Puerto Rico; Laman A. Gray, Louisville, Ky.; Joseph D. Guess, Greenville, S. C.; G. W. Gustafson, Indianapolis, Ind.; Samuel C. Gwynne, Worcester, Mass.; Reynold L. Haas, Ann Arbor, Mich.; Bernard J. Hanley, Los Angeles, Calif.; John W. Harris, Madison, Wis.; Albert F. Hayes, St. Paul, Minn.; Orvan W. Hes. New Haven, Conn.; H. C. Hesseltine, Chicago, Ill.; Wilbur E. Hoffman, Charleston, W. Va.; Emil G. Holmstrom, Salt Lake City, Utah; John C. Hope, Jr., Mobile, Ala.; E. C. Hughes, Syracuse, N. Y.; Parker K. Hughes, Des Moines, Iowa; J. Wilson Huston, Key West, Fla.; J. D. James, Springfield, Mo.; Lewis P. James, Hartford, Conn.; Brock D. Jones, Jr., Norfolk, Va.; Robert A. Johnston, Houston, Texas; Jack R. Jones, Baton Rouge, La.; Scott S. Jones, Tacoma, Wash.; George Kamperman, Detroit, Mich.; Joseph E. Kanatser, Wichita Falls, Texas; Harry M. Kanner, Sacramento, Calif.; Richard J. Karberg, Lafayette, Ind.; E. L. King, New Orleans, La.; Walter J. Larkin, Scranton, Pa.; Robert N. Lord, Manchester, N. H.; Andrew A. Marchetti, Washington, D. C.; Harvey B. Matthews, Brooklyn, N. Y.; Lyman W. Mason, Denver, Colo.; William B. McGee, San Diego, Calif.; Charles E. McLennan, San Francisco, Calif.; Louis A. McRae, Albuquerque, N. Mex.; William F. Mengert, Dallas, Texas; George W. Mitchell, Jr., Boston, Mass.; Roy W. Mohler, Philadelphia, Pa.; Truman N. Morris, Austin, Texas; Theodore Neustaedter, New York City; Robert L. Newman, Kansas City, Kan.; John McI. Nokes, Charlottesville, Va.; Richard Paddock, St. Louis, Mo.; Alfred L. Potter, Providence, R. I.; John D. Preece, Trenton, N. J.; Paul A. Raber, Decatur, Ill.; Clyde L. Randall, Buffalo, N. Y.; Herman W. Rannels, Lancaster, Pa.; Leon Reidenberg, Reading, Pa.; Verne J. Reynolds, Boise, Ida.; Roger B. Scott, Cleveland, Ohio; E. F. Shay, Fall River, Mass.; Walter H. Simmons, Jr., Jackson, Miss.; Shirley R. Snow, Jr., Rochester, N. Y.; Frederick J. Stoddard, Milwaukee, Wis.; Irving J. Strumpf, Ancon, Panama Canal Zone; Ralph E. Tafel, Pittsburgh, Pa.; F. W. Tamblyn, Lansing, Mich.; Athol B. Thompson, Grand Rapids, Mich.; Clarence E. Toshach, Saginaw, Mich.; Richard Torpin, Augusta, Ga.; Charles B. Upshaw, Atlanta, Ga.; D. D. Wall, San Angelo, Texas; Cecil E. Warde, Memphis, Tenn.; Hudnall H. Ware, Jr., Richmond, Va.; Alven M. Weil, Akron, Ohio; Lester A. Wilson, Charleston, S. C.

The next scheduled examinations, Part II (oral and pathological), for all candidates will be held at the Edgewater Beach Hotel, Chicago, Ill., by the entire Board from May 17 through May 24, 1953. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examinations.

Applications for Certification for the 1954 (Part I) examinations are now being accepted, and candidates are urged to make such application sometime in August or September. This would be of great help in expediting processing of these applications.

Candidates applying for admission to the Part I examinations are reminded that the Board now requires them to submit a list of all patients for whom they have been *solely* responsible admitted to the hospitals where they practice, for the year preceding their application or the year prior to their request for reopening of their application, with the diagnosis, pathological diagnosis, nature of treatment, and end result. This list should be submitted at the time application is made or at the time request for reopening of an application is sent, and it should be on 8½ by 11 inch paper, unbound, and contain the name of the candidate and his address.

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Southern Society of Cancer Cytology

The first scientific meeting of this organization is planned to be held in Atlanta, Georgia, in November, 1953, simultaneously with the session of the Southern Medical Society. For further information apply to Dr. J. Ernest Ayre, Secretary, Dade County Cancer Institute, 1155 N.W. 14th Street, Miami, Fla.

Erratum

The following corrections should be made in the article, "The Contracted Upper Midpelvis," by Samuel Hanson in the February, 1953, issue of the Journal, pp. 290-293:

The general average width of the upper midplane is 11.6 cm., and its average area is 149.6 sq. cm. (page 291, third paragraph).

Case 3,	Table I, Inlet Area	140.4 sq. cm.
Case 12,	Table I, Inlet Area	136.1 sq. cm.
Case 13,	Table I, Inlet Area	128.8 sq. cm.
	Upper Midpelvis Trans.	10.5 cm.
	Upper Midpelvis Area	123.9 sq. cm.
Case 1,	Table II, Upper Midpelvis Area	111.3 sq. cm.
Case 7,	Table II, Upper Midpelvis Trans.	11.3 cm.
	Upper Midpelvis Area	146.9 sq. cm.
Case 10,	Table II, Upper Midpelvis Area	126.0 sq. cm.
Case 12,	Table II, Upper Midpelvis Trans.	10.4 cm.
	Upper Midpelvis Area	114.4 sq. cm.
Case 13,	Table II, Upper Midpelvis Area	129.3 sq. cm.